THE UNIVERSITY OF ALBERTA

STUDIES ON THE CYCLIZATION OF 1,4- AND 1,5-DIKETONES

by

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A THESIS

SUBMITTED TO THE FACULTY OF GRADUATE STUDIES AND RESEARCH

IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE

OF MASTER OF SCIENCE

DEPARTMENT OF CHEMISTRY

EDMONTON, ALBERTA

FALL, 1981

THE UNIVERSITY OF ALBERTA

RELEASE FORM

NAME OF AUTHOR RAKHSHANDEH FATHI-AFSHAR

TITLE OF THESIS STUDIES ON THE CYCLIZATION OF 1,4- AND 1,5-DIKETONES

DEGREE FOR WHICH THESIS WAS PRESENTED M.Sc.

YEAR THIS DEGREE GRANTED 1981

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STUDIES ON THE CYCLIZATION OF 1,4- AND 1,5-DIKETONES

submitted by RAKHSHANDEH FATHI-AFSHAR in partial fulfilment of the requirements for the degree of Master of Science.

John Hooz
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ABSTRACT

A study was undertaken of the hydrolysis-cyclization reaction of 2-[γ-n-butyl(phenyl)thiocrotyl]cyclohexanones using titanium tetrachloride. In this investigation, it was shown that the predominant formation of octalone system is most likely due to an intramolecular nucleophilic attack of vinyl sulfide on the carbonyl function. It was also noticed that the role of titanium tetrachloride is to provide the acidity required for this cyclocondensation (through its reaction with acetic acid), rather than directing the cyclization by "Ti chelation".

Application of this methodology was extended to examine the cyclization of alkyl and phenyl vinyl sulfides derived from 2,5-nonanedione. Treatment of these vinyl sulfides with titanium tetrachloride led to their hydrolysis to the original 1,4-diketone, and none of the expected cyclopentenones were observed.

The dehydrosulfenylation of a number of monosulfoxides derived from thioketals was examined. It was noticed that for most cases the ratios of the terminal to internal regioisomers of the vinyl sulfides produced, were more than unity. As a consequence of addition of potassium carbonate, these ratios and the yield of vinyl sulfides were increased to a great extent.

Finally a direct comparison was made between the attempted cyclization of 2,5-nonanedione and 2,6-undecanedione under different reaction conditions.

ACKNOWLEDGEMENTS

I would like to express my deep gratitude and sincere appreciation to Professor John Hooz for his patience, excellent guidance, and supervision during the course of this investigation.

My thanks also go to the members of the research group with whom I have had the pleasure to work: Drs. R. Mortimer, J. Oudenes, F. Skinner, A. Nakinishi, and M. Rodriguez.

Furthermore, I would like to acknowledge:

The technical staff of the Department of Chemistry for the determination of spectra.

My husband M.H. Saeedi for his helpful ideas and moral support.

Ms. D. Dowhaniuk for her excellent work in typing the manuscript.

Mrs. A. Jourdan for the love she gave my son during the past year, which enabled me to finish my studies.

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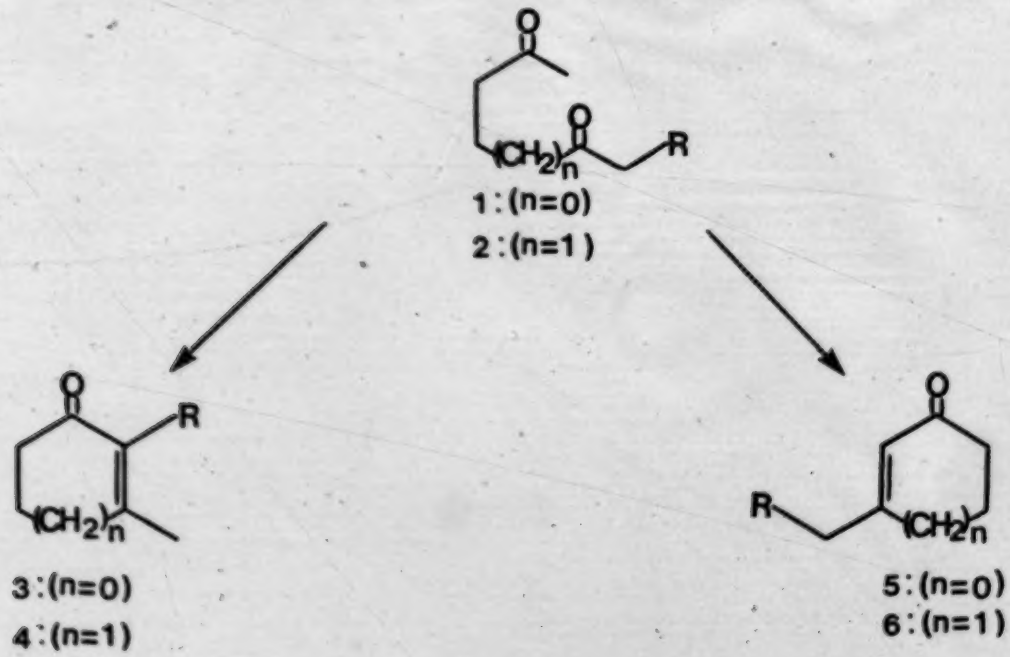
INTRODUCTION

The intramolecular aldol condensation is an important pathway for the synthesis of cycloenones. Construction of six- or five-membered rings with the proper functional groups and the right substitution pattern is essential in the synthesis of a great number of natural products.

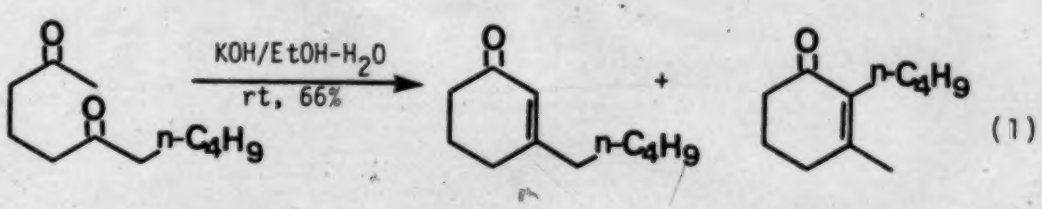
Several groups have been involved in the study of the factors which influence the direction of cyclization of acyclic unsymmetrical diketones of the type $RCH_2CO(CH_2)_nCOCH_3$.

In principle cyclization of 1,4- and 1,5-diketones such as 1 and 2 in either acid or base could give rise to tetrasubstituted enones 3 and 4 or trisubstituted enones 5 and 6.



In practice cyclization of 1,5-diketones yield both products 4 and 6 for most cases. The ratio of the two products depends on the reaction conditions employed and on the nature of the R group.

Cyclization of 2,6-undecanedione 7 has been studied under different reaction conditions. According to Danishefsky and Zimmer,[1] reaction of dione 7 with potassium hydroxide at room temperature produces both tri- and tetrasubstituted cyclohexenones 8 and 9 as shown in equation 1.



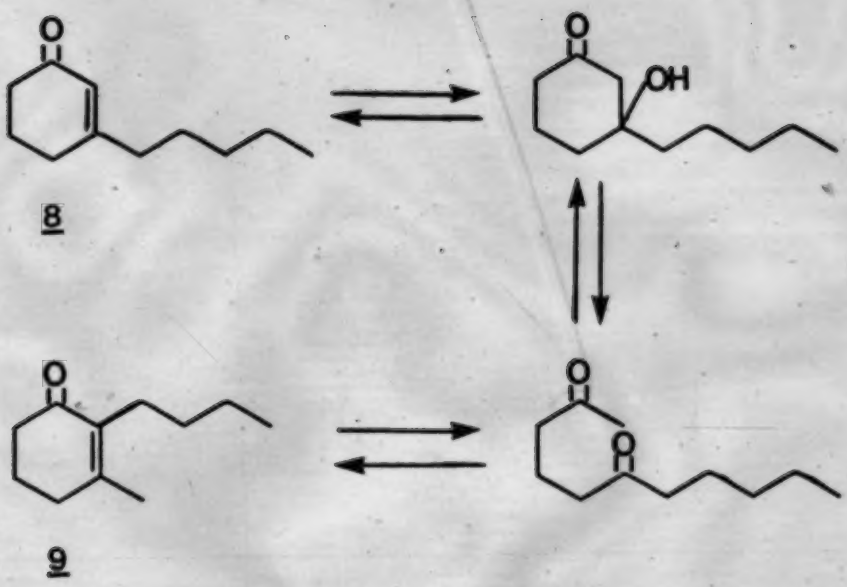
(1)

7 8 9

(60:40)

Under more forcing conditions (reflux) it has been demonstrated by Stork and Borch[2] that only enone 9 is produced in 82% yield to the apparent exclusion of compound 8.

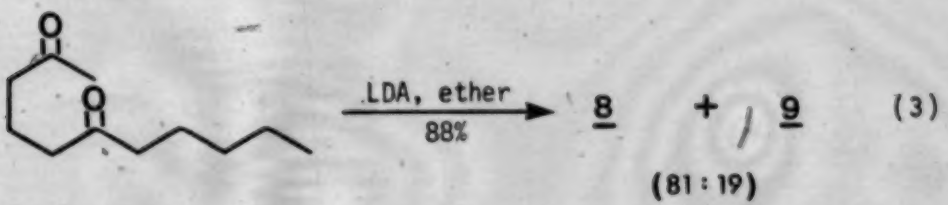
It was also shown[1] that cyclohexenone 8 could be isomerized to 9 in aqueous alkali under reflux conditions presumably by hydration and retro-aldol followed by aldol cyclization[3] (eq. 2).



8 (2) 9

The simplest interpretation for the observed results is that the formation of tetrasubstituted products at elevated temperatures is the consequence of thermodynamic equilibration.

Kinetically controlled cyclocondensation of dione 7 has been examined by Lacheveque and co-workers.[4] Using lithium diisopropylamide to generate the enolate anion the yield of enone 8 increased to some extent (eq. 3).

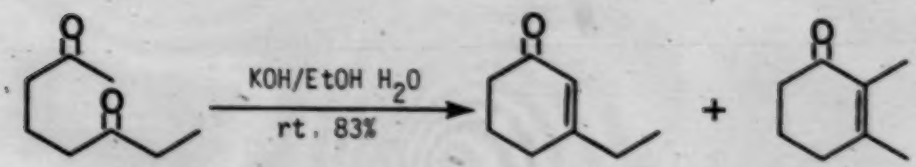


7 (3)

Acid-induced (H_2SO_4) cyclodehydration of 7 has also

been studied,[4] and the result is the predominant formation of tetrasubstituted enone 9.

Rather different results are observed from the room temperature cyclization of 2,6-octanedione 10 under basic conditions. Danishefsky and co-workers[1,5] have reported that cyclization of dione 10 under these conditions favors the tetrasubstituted cyclohexenone 12 overwhelmingly (eq. 4).



(4)

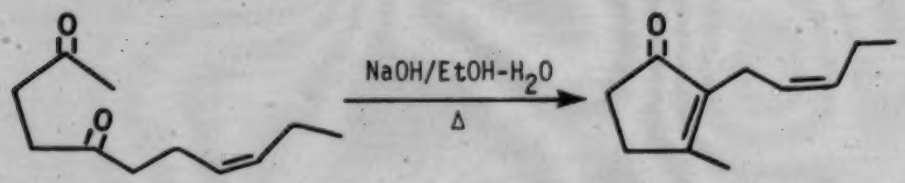
10 11 (5:95) 12

Lacey[3] has shown that 3-ethylcyclohex-2-enone 11 isomerizes under basic conditions (reflux) to a 93:7 mixture of 2,3-dimethylcyclohexenone and 11.

The differences observed between the base-catalyzed cyclization of diones 7 and 10 under similar reaction conditions, however, remain unexplained.

On the other hand, results obtained from the cyclization of 1,4-diketones have proven to be rather different from that of 1,5-diketones. For example, 2,5-diones of type 1 fail to cyclize under acidic conditions[6] (i.e., only starting material is recovered), and alkaline treatment[6,7] of compounds of type 1 yield exclusively tetra-

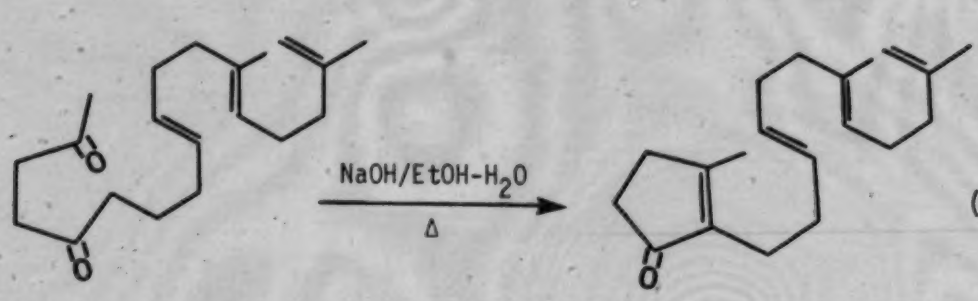
substituted enones of type 3 to the apparent exclusion of cyclization to 5. This finding has been extensively used in the synthesis of cis-jasmone[7] (eq. 5), dihydro-



(5)

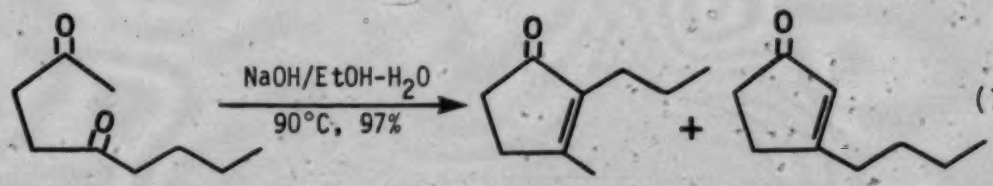
cis-Jasmone

jasmone,[8] and also in the well-known synthesis of steroids by Johnson and co-workers[9] (eq. 6).



(6)

The only documented case in which a trisubstituted cyclopentenone is formed as a minor product from cyclodehydration of compounds of general formula 1 has been reported by McCurry and Singh.[10] Reaction of dione 13 with alkali (90°C) yields cyclopentenones 14 and 15 as shown in equation 7.



(7)

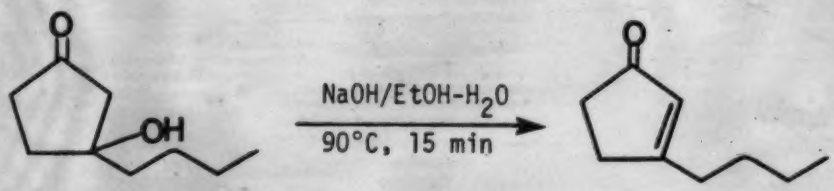
13 14 15

(94:6)

However, Danishefsky and co-workers[1] have examined this reaction at room temperature and the result was again formation of compound 14 as the only product in 85% yield, and none of the enone 15 was detected.

Although this reaction resembles the reaction of 2,6-dione 10 with base, a mechanistic study of aldolization of 1,4-diketones[10,11] indicates that there is a major difference in the directionality of cyclization of 1,5- and 1,4-diketones under identical conditions.

McCurry[10] has examined the reversibility of the formation of enone 15 under the reaction conditions which serve to cyclize dione 13, and has noticed that a high yield (>95%) of starting material is recovered, and none of the cyclopentenone 14 is detected. Interestingly, aldol 16 also failed to yield enone 14 when submitted to the cyclization conditions, and the sole detectable product was compound 15 (eq. 8).



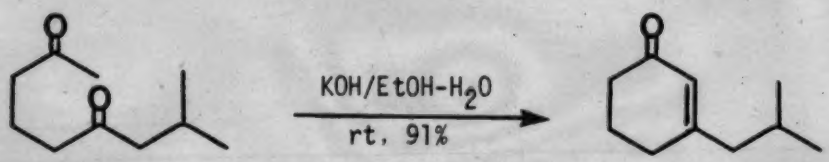
(8)

16 15

These results demonstrate the dramatic difference between 1,5- and 1,4-diketones cyclizations, since formation of trisubstituted cyclohexenones have been shown to

be reversible in most cases (eq. 2).

There have been no systematic studies on the effect of R groups on the cyclization of 1,4-diketones. However, Danishefsky has studied the effect of several R groups on the product distribution of cyclohexenones. In this connection, cyclization of diketone 17 under basic condition at room temperature produces trisubstituted enone 18 to the apparent exclusion of the tetrasubstituted product (eq. 9).



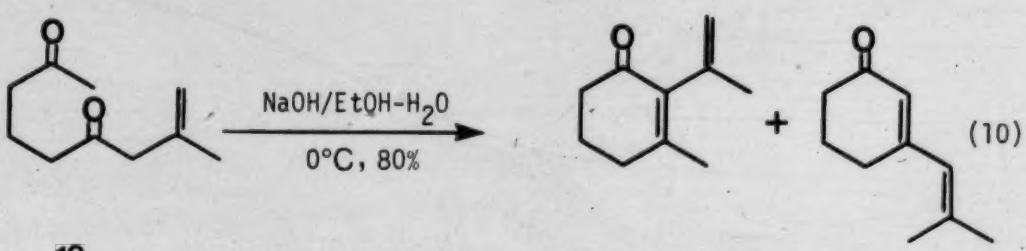
(9)

17 18

The effects of branching are dramatically seen in the comparison of the results of base-catalyzed aldol cyclization of diketones 7 and 10 at room temperature with those of dione 17.

The nature of the effect of carbon branching on product distribution is not known in detail. It may be that due to steric effects, by retarding the formation of the β-aldol precursors of type 4 product. Alternatively, it may be that there is some retardation of the final dehydration step. An interesting case in this regard is reported by Rouessac and Alexandre.[12] The sig-

nificance of the branching effect is nicely illustrated in the base-catalyzed cyclization of 8-methylnon-8-ene-2,6 dione 19 (eq. 10).



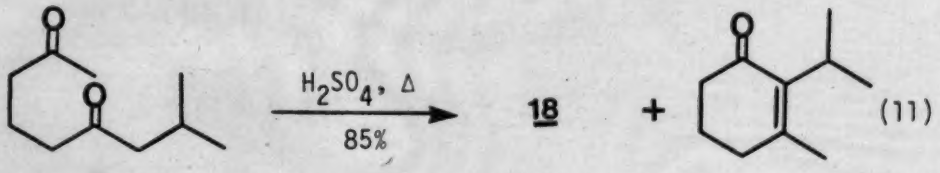
(10)

19

(60:40)

Even though the acidity factors must strongly favor formation of the tetrasubstituted isomer, the ratio is in fact close to unity.

The effect of branching is also seen in the acid-catalyzed cyclization of compound 17, in which almost equal amounts of the two products are obtained (eq. 11).



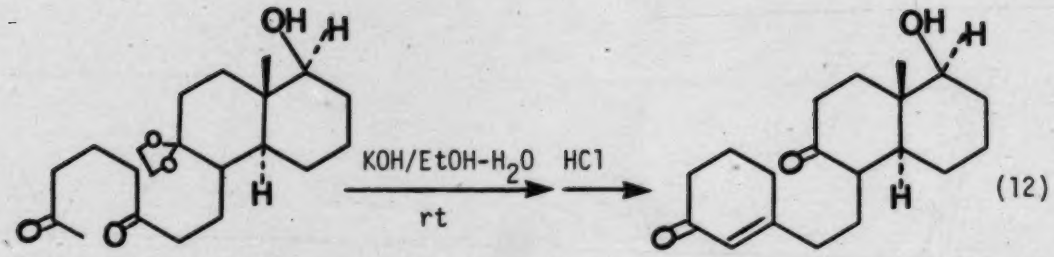
(11)

17

20

(55:45)

Information available from these and several other studies[1,5,13] on the effect of carbon branching on the product distribution has been utilized[1] in the synthesis of the A ring of the steroids (eq. 12).

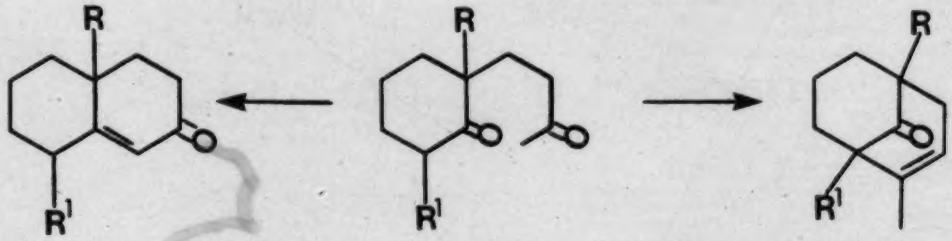


(12)

83%

One of the most widely used applications of the intramolecular aldol condensation of 1,5-diketones has been in the field of the synthesis of octalone systems. Construction of these compounds has been extensively studied in work directed toward the synthesis of such complex natural products as steroids, terpenes, and alkaloids.

In principle acid or base catalyzed cyclization of diones 21 could give rise to octalones 22 or bicyclo-



22 21 23

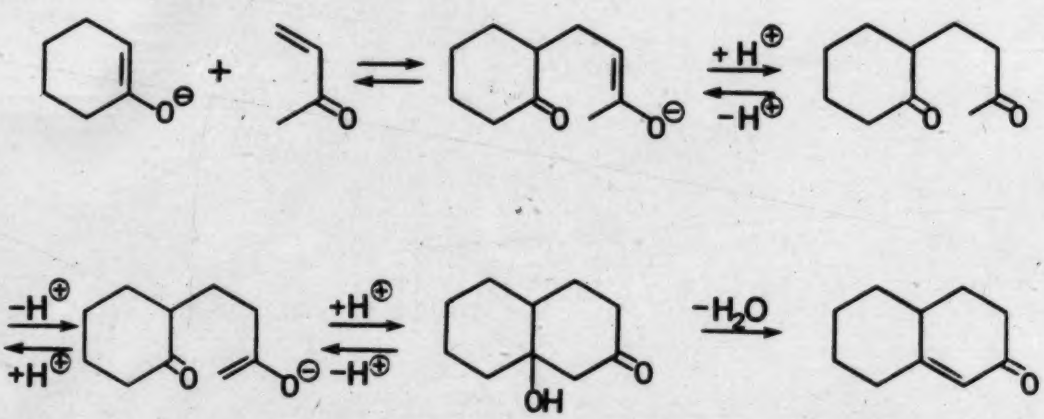
[3.3.1]nonanones 23. However, in all these studies the main goal has been to suppress the formation of bridged

bicyclic products of the type 23.

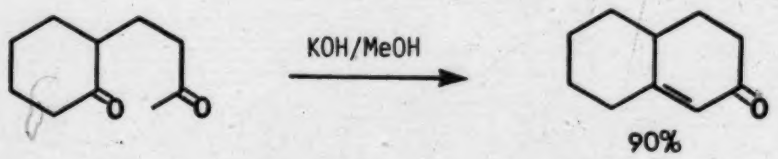
Among all the known methods for the construction of octalone systems, the Robinson annelation reaction[14,15] holds a position of particular importance.

This involves the base-catalyzed Michael addition of a ketone to methyl vinyl ketone followed by base-catalyzed aldol condensation (Scheme I).

Scheme I



It has been shown that[16,17,18] regardless of the nature of R and R^1, cyclization of diones of type 21 under basic conditions yield only the corresponding octalone systems (eq. 13-16), with the apparent exclusion of interference from cyclization to bridged bicyclic products. Thus, to the extent that the Michael addition does occur, the octalone products would be obtained. However, the Robinson annelation is subject to several restrictions prior to the cyclization step, such as



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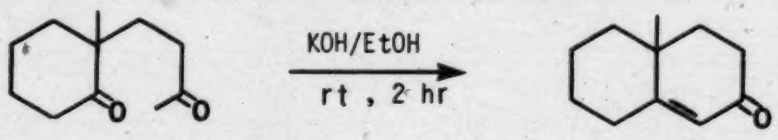

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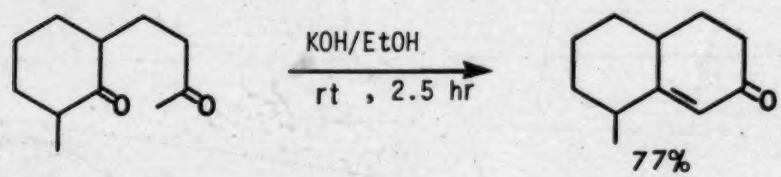

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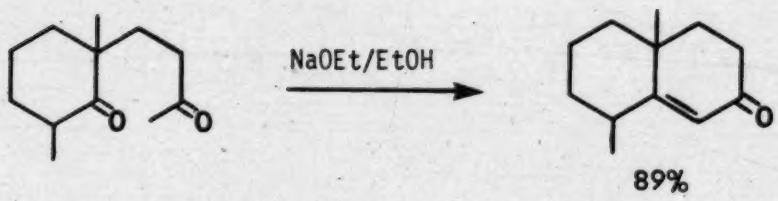


(16)

24 **25**

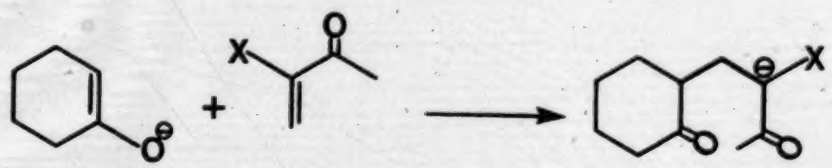
polymerization of methyl vinyl ketone, the problem of controlling the site of alkylation in unsymmetric ketones, and finally the problem of dialkylation.

The problem of polymerization of methyl vinyl ketone was overcome in part by the use of Mannich bases,[15,19,20] and β-haloketones[21] to generate the Michael acceptor *in situ*.

To control the regiochemistry in the initial step of the sequence, the use of enamines,[22] activating or directing groups,[23,24] and blocking groups have been

extensively studied, and have been proved to be useful in many cases.

Dialkylation could be avoided using α-substituted vinyl ketones (i.e., 26) in which the substituent is able to stabilize the initial Michael adduct 27 (eq. 17).

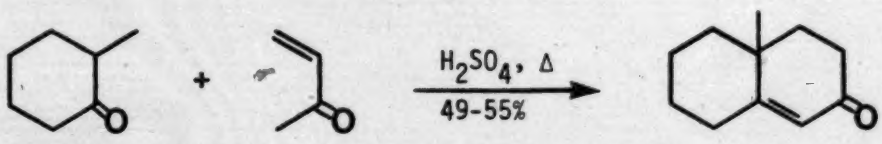


(17)

26 27

Satisfactory results are obtained from cases where X is $COOR$[25,26] or $SiEt_3$.[27,28,29] Similarly the use of a methyl vinyl ketone-metal complex[30] in annelation has been helpful in diminishing the dialkylation problem.

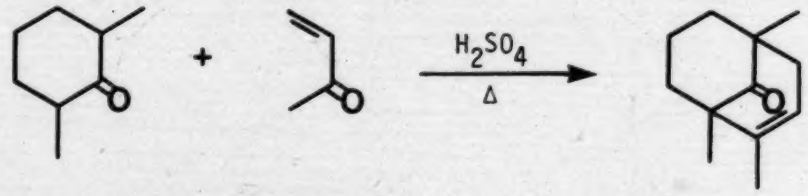
Another modification of the original Robinson annelation has been introduced by Heathcock and Ellis.[31] These workers have found that high yields of octalone products may be obtained under conditions of acid catalysis (H_2SO_4). Although this reaction offers a distinct advantage for the preparation of octalones derived from 2-methylcyclohexanones (eq. 18), it fails in the case of 2,6-dimethyl-



(18)

cyclohexanone, and the bicyclo[3.3.1]nonenone 28 is

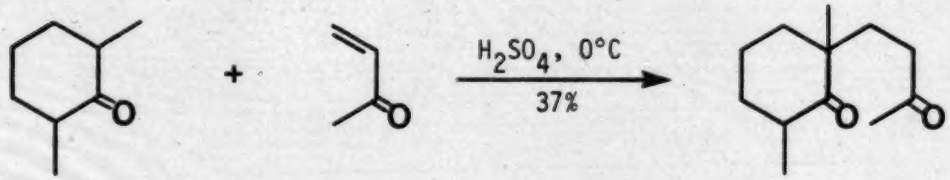
isolated as the only product (eq. 19).



(19)

28

Still and co-workers[16] have discovered that the reaction can be stopped prior to the final aldol condensation, if it is performed at 0°C (eq. 20).

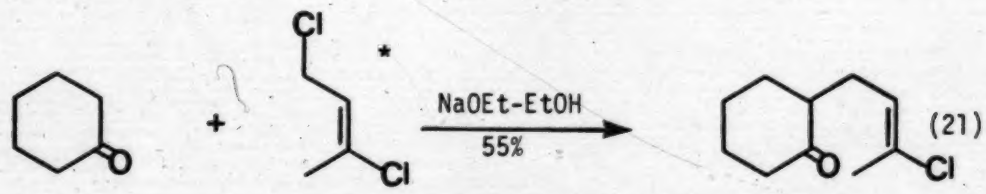


(20)

24

Another modification has been the use of electrophiles with masked carbonyl functions such as a chloromethylisoxazole derivative;[32] 3-trimethylsilyl-2-butenyl iodide,[33] and t-butyl γ-iodotiglate.[34]

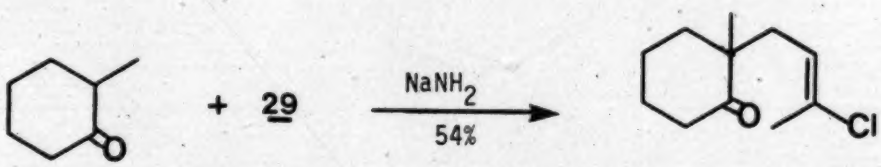
A widely used "3-oxobutyl" equivalent is 1,3-dichloro-2-butene, 29, the Wichterle reagent.[35] According to Julia and co-workers,[36] alkylation of simple ketones, eg. cyclohexanone, affords the alkylated product in moderate yield (eq. 21).



(21)

29

Marshall and Schaeffer[17] used this reaction to alkylate 2-methylcyclohexanone (eq. 22).



(22)

The major drawback of this sequence is that the acidic conditions necessary to hydrolyze the vinyl chloride also results in formation of undesired bridged bicyclic compounds,[17,36] as indicated in Scheme II. This is especially severe for 2,6-dimethyl-2-(γ-chlorocrotyl)-cyclohexanone, since the acid hydrolysis of this compound affords none of the desired diketone; instead, the bridged product, 1,2,5-trimethylbicyclo[3.3.1]non-2-en-9-one, is exclusively formed.

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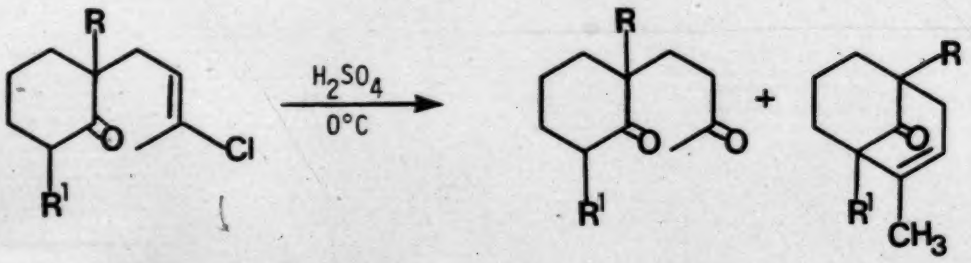
* The alkylating agent is a mixture of diastereoisomers. For convenience, it is written as a single isomer, as are all the alkylation products.

Scheme II

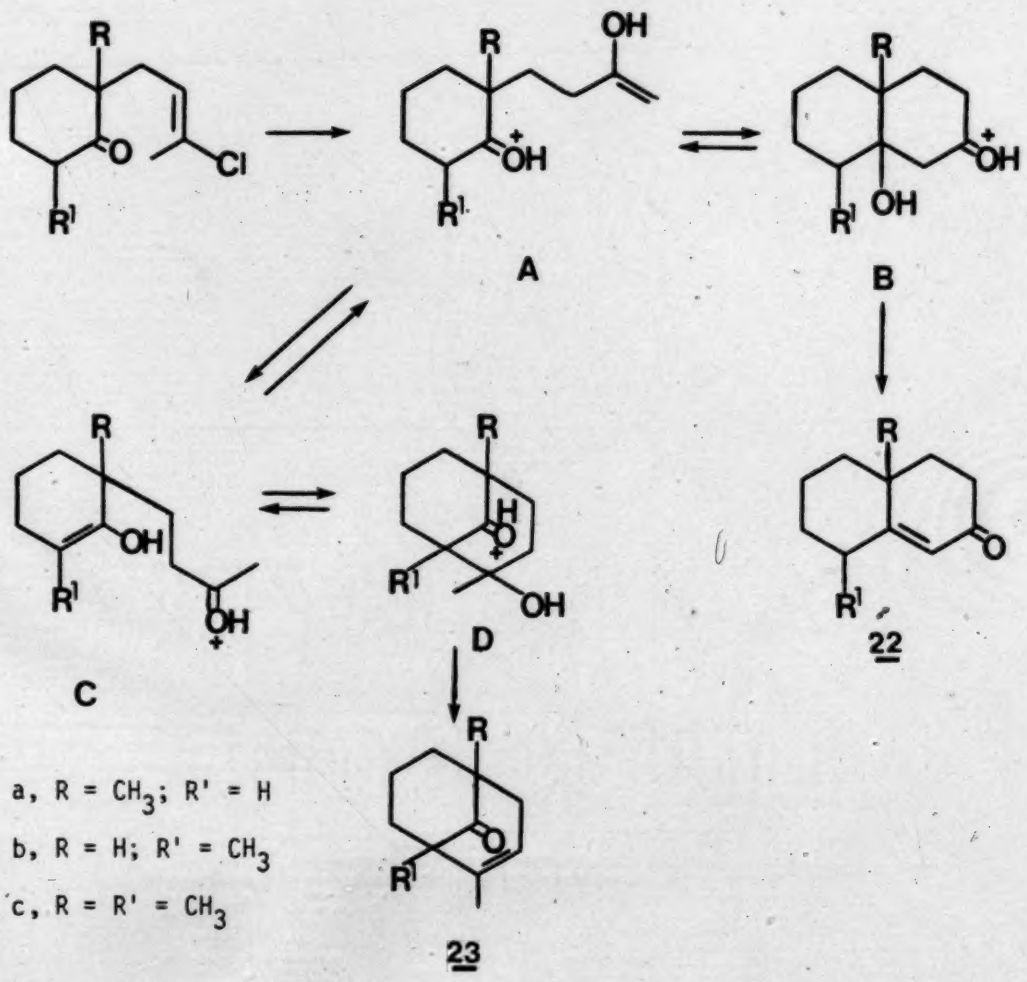


R	R^1		
Me	H	47%	11%
H	Me	53%	8%
Me	Me	0%	93%

These findings provide an interesting contrast with the results obtained by Julia[36] on the hydrolysis of 2-(γ-chlorocrotyl)cyclohexanone ($R = R^1 = H$). In this case a mixture was formed in which the bicyclo-[4.4.0] and the bicyclo[3.3.1] products were formed in nearly equal amounts.

Marshall has suggested that two factors control the direction of the cyclization (Scheme III):

Scheme III



a, R = CH_3; R' = H

b, R = H; R' = CH_3

c, R = R' = CH_3

the steric environment of the cyclohexanone carbonyl grouping, and the difference in stability of the enols A and C (due to hyperconjugative stabilization). Thus, it is suggested that methyl groups in the 2- and 6-position on the cyclohexanone ring should retard the reaction A → B. On the other hand, both a 2- and 6-methyl group might be expected to facilitate the reaction leading to

the bicyclo[3.3.1] product (C → D). The energy difference between the conformer with an axial butanone side chain (needed for the formation of bridged product Da) and the equatorial side-chain conformer (where bridging is prohibited by steric effects) should be smaller in the 2-methyl-2-(3-oxobutyl)cyclohexanone intermediate Ca than in the corresponding desmethylanalog C (R = R' = H) where the equatorial side chain should be greatly favored. Bridged product 23 might therefore be more easily formed.

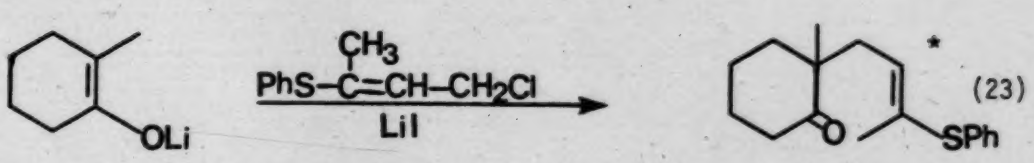
The use of titanium tetrachloride as a milder hydrolyzing agent to hydrolyze vinyl chlorides has been explored by Mukaiyama and co-workers,[37] but this modification does not offer any advantage over the use of sulfuric acid. Although none of the cyclic products are formed, the yield of the diketone obtained, however, remains low.

Two modifications[17,38] have been introduced to overcome the problems involved in the hydrolysis step of vinyl chlorides, nonetheless they involve rather lengthy procedures.

In search of a more effective approach to construct the octalone systems, the use of γ-alkyl(phenyl)thiocrotyl chloride systems as an "oxobutyl" equivalent has been investigated in this laboratory.[39]

The result is an alternative to the Michael-Robinson process to provide a "3-oxobutyl" equivalent from

readily available starting materials, and is also active toward regiospecifically generated enolates. One example of this reaction is shown in equation 23.

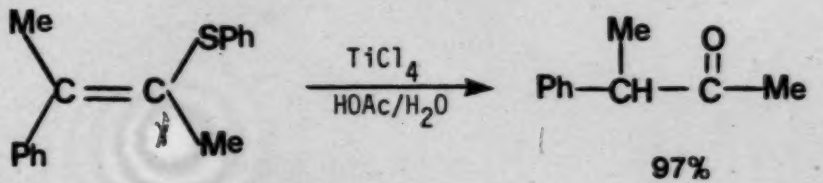


(23)

85%

It was necessary to avoid the use of strongly acidic hydrolyzing conditions, since formation of the dione system may be followed by cyclization to the undesired bridged bicyclic products, as shown earlier in the case of vinyl chlorides.[17]

In search of a mild hydrolyzing agent Mukaiyama's procedure was investigated, and proved to be effective. According to this method vinyl sulfides are hydrolyzed to the corresponding ketones in high yields using titanium tetrachloride (eq. 24).



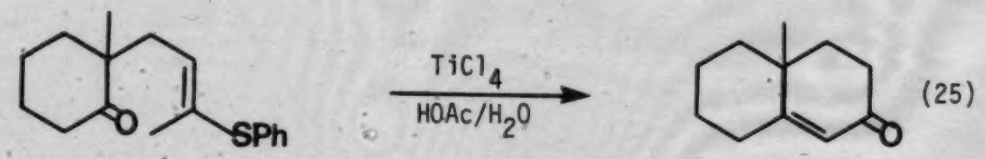
(24)

97%

---

* This product consists of both Z and E geometric isomers. For convenience, it is written as a single isomer, as all the other similar vinyl sulfides.

The results obtained from the hydrolysis of several γ-thiocrotylcyclohexanones utilizing this procedure proved interesting, since, instead of hydrolysis to the corresponding diketones, simultaneous cyclization to the desired octalone system was also effected (eq. 25).

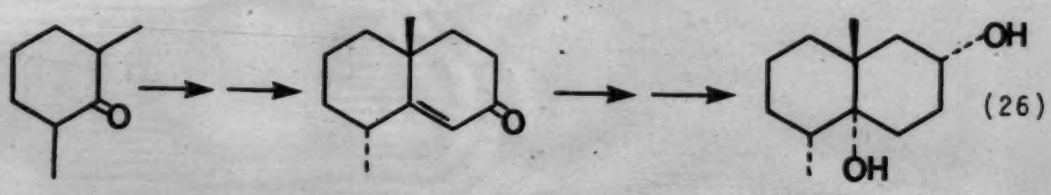


(25)

63%

These observations are in contrast to the results obtained by Marshall[17] from the hydrolysis of the corresponding 2-(γ-chlorocrotyl)cyclohexanones in sulfuric acid, where in some cases undesired bridged bicyclic compounds are obtained exclusively.

Using this scheme, the preparation of the more troublesome octalones, such as 8,10-dimethyl-1(9)-octal-2-one, becomes possible in two steps starting from the ketone, and this has been utilized in the synthesis of (±)-cybullol, one of the metabolites of bird's nest fungi, by Ayer and co-workers[41] (eq. 26).



(26)

(±)-Cybullol

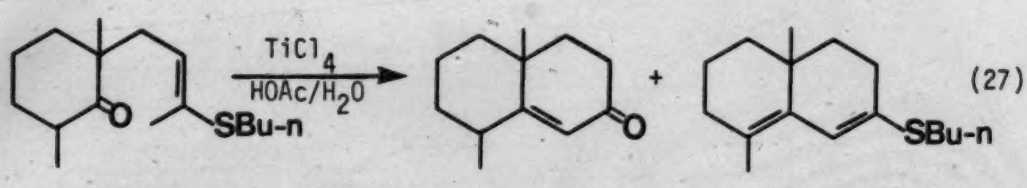
This reaction holds a particular place of importance, not only because it offers an efficient method to synthesize the octalone systems, but also because of the regiospecificity observed at the cyclization step, since it was shown that in most cases acid catalyzed aldol condensation of 1,5-diketones of the type 21 lead to the formation of bridged bicyclic products to some extent, if not exclusively.

In light of these developments (i.e. preparation of trisubstituted cyclohexenones via cyclization of the corresponding vinyl sulfides), the possibility arose of applying this method to the cyclization of other diones such as acyclic 1,5- and 1,4-diketones.

Therefore the purpose of this work was to investigate in more detail the hydrolysis-cyclization of the vinyl sulfides which lead to the formation of octalone systems, and also to utilize this methodology to examine the cyclization of unsymmetrical acyclic diketones.

RESULTS AND DISCUSSION

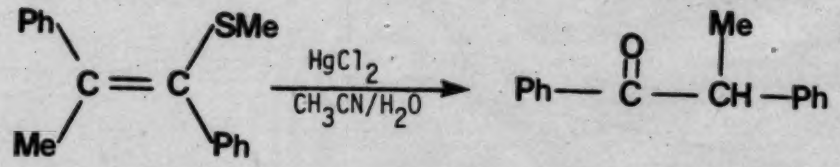
To study the reaction of ketovinyl sulfides with titanium tetrachloride which lead to the formation of octalone systems, the hydrolysis-cyclization reaction of 2,6-dimethyl-2-(γ-n-butylthiocrotyl)cyclohexanone 30 was chosen as a model. The original procedure[40] for $TiCl_4$ hydrolysis of vinyl sulfides employed three different solvents: acetic acid, acetonitrile, and methylene chloride. However, close examination (glpc) of the $TiCl_4$-promoted hydrolysis of compound 30 in solvents other than acetic acid indicated that a complex mixture of products were formed.[39] In contrast, reaction of this compound with 2.4 equivalent of $TiCl_4$ in acetic acid and water at room temperature produced diene sulfide 31 in 30% yield as well as 59% of the octalone 25 (eq. 27).



(27)

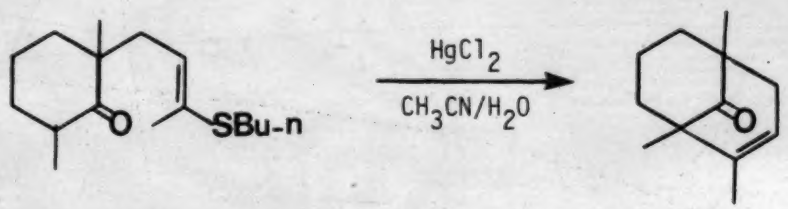
30 25 31

It is known[42] that mercuric chloride in aqueous acetonitrile hydrolyzes vinyl sulfides to the corresponding ketones (eq. 28). Using this procedure compound 30



(28)

was also hydrolyzed[39] with $HgCl_2$ at room temperature, but instead of the corresponding diketone, the bridged bicyclic compound 28 was produced as the only product in 90% yield (eq. 29).

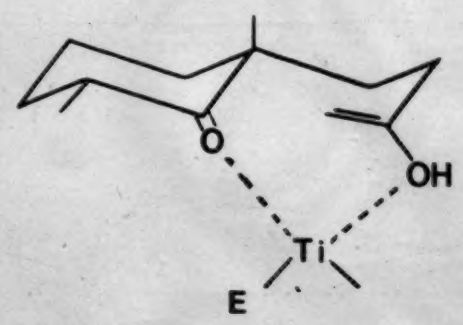


(29)

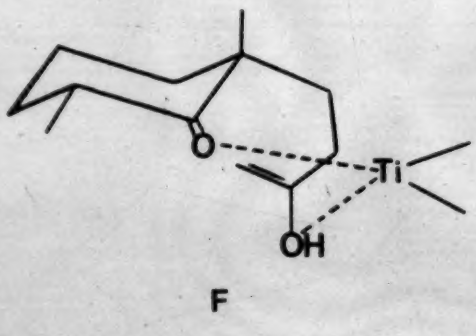
30 28

It was also shown that addition of one equivalent of calcium carbonate prevents the hydrolysis, as well as the cyclization, and starting material was the only isolable product.

Based on information available at the time of these studies, as well as inspection of Dreiding molecular models, it was suggested that the predominant formation of the bicyclic[4.4.0]decanone system in the reaction of compound 30 with titanium tetrachloride is possibly due to the formation of an intermediate, eight-membered cyclic titanium chelate, E and/or F. Inspection of molecular

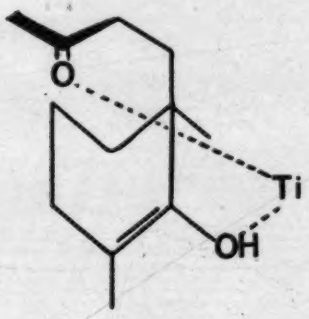


E

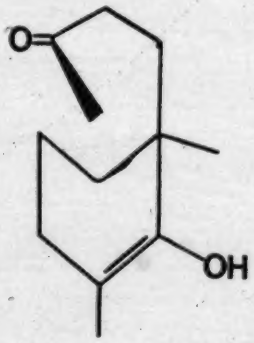


F

models for two other possible conformers (G and H) which would lead to the bridged bicyclic compound indicated that conformer G lacks sufficient overlap between the



G

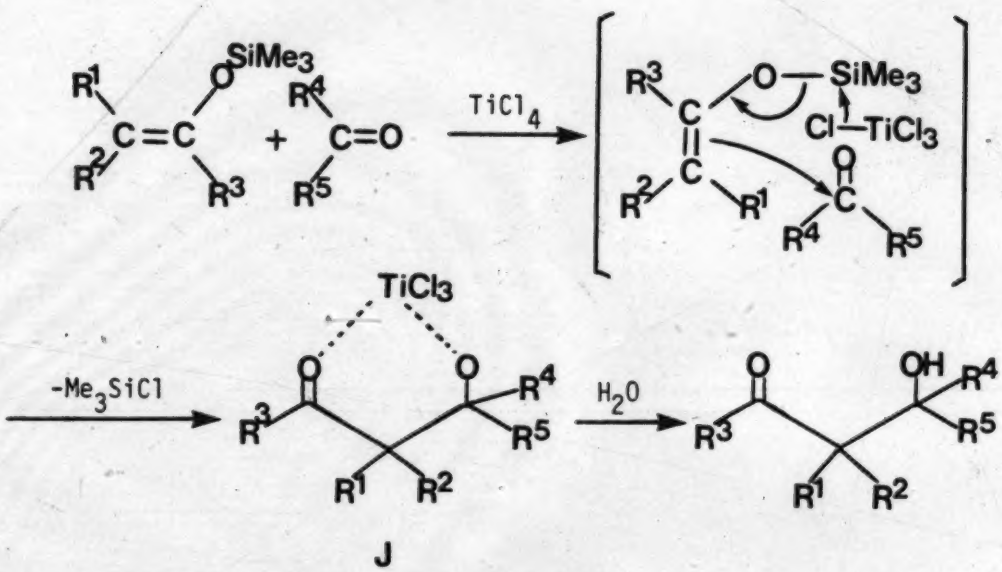


H

π system of the carbonyl group and the double bond of the enol (they almost bisect each other), and conformer H was rejected because the carbonyl and hydroxyl group are too far apart for effective chelation with titanium. Therefore, formation of octalone 25 was best explained by proceeding via conformers E and/or F.

This type of chelation of titanium had other precedents. For example, Mukaiyama[43] had shown that in crossed-aldol reactions, titanium strongly activates the reaction of silyl enol ethers with carbonyl compounds (Scheme IV), and suggested that formation of chelate J is a strong driving force for the formation of the aldol product.

Scheme IV



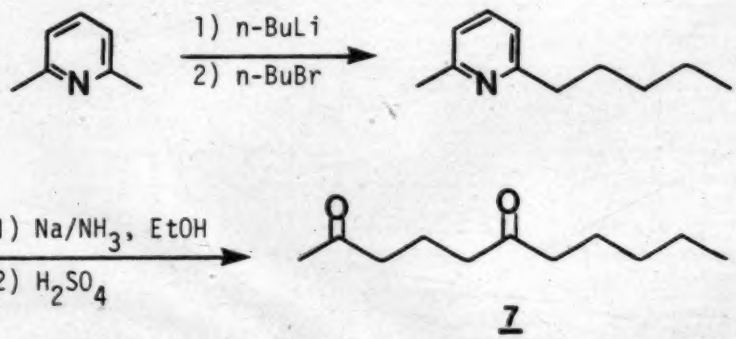
J

Although predominant formation of the octalone system could be rationalized by consideration of conformers E and/or F, no explanation was offered for the use of acetic acid as the only solvent to successfully achieve this type of cyclization.

If chelation of titanium with the dione (produced from the hydrolysis of compound 30) was the responsible factor for formation of the octalone system, then the same results were to be expected if diketone 24 was reacted wtih $TiCl_4$ independently. Having this in mind, the reaction of 2,6-dimethyl-2-(3-oxobutyl)cyclohexanone 24 with $TiCl_4$ was investigated. Also as a direct consequence of the results observed from hydrolysis of

ketovinyl sulfides,[39] an investigation of the reactions of other unsymmetrical acyclic diketones, such as 2,6-undecanedione, and 2,5-nonanedione with $TiCl_4$ was attempted.

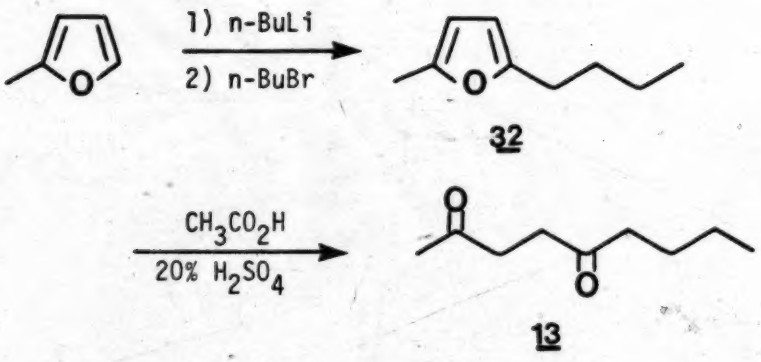
To prepare diketone 7, 2,6-lutidine was alkylated[1] using n-butyllithium and n-butyl bromide in ether to produce 66% of the 2,6-alkylated pyridine derivative. This was followed by a Birch reduction, and hydrolytic opening of the dihydropyridine to provide 65% of diketone 7 (eq. 30).



(30)

7

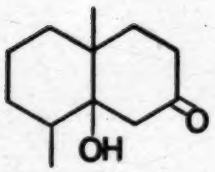
Preparation of diketone 13 was achieved in two steps from 2-methylfuran, by first alkylating with n-butyl bromide[44,45,46] (70%) to yield 2-methyl-5-n-butylfuran 32, followed by hydrolysis[45,46] to 2,5-nonanedione 13 in 80% yield after distillation (eq. 31).



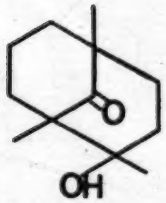
(31)

Finally 2,6-dimethyl-2-(3-oxobutyl)cyclohexanone was prepared according to Still's procedure[16] (eq. 20) in 40% yield from the reaction of 2,6-dimethylcyclohexanone with methyl vinyl ketone in benzene. Subsequent treatment of this dione with titanium tetrachloride in acetic acid, under the same conditions used for the hydrolysis-cyclization reaction of compound 30, yielded one major product (79%). This could be separated from unreacted starting material (8%) using column chromatography on silica gel (elution with Skelly B-chloroform).

The infrared spectrum of the product, however, showed no evidence for the expected conjugated enone. Instead there were absorptions at 3510 and 1710 cm^{-1} (characteristic of a ketol). Mass sepctral analysis indicated a molecular weight of 196. Two possible ketol structures (33 and 34) are compatible with these data. However the n.m.r. spectrum (90 MHz, $CDCl_3$) lacked a doublet between 0.9-1.0 (3 H), which is characteristic of the methyl group attached to the secondary carbon atom in

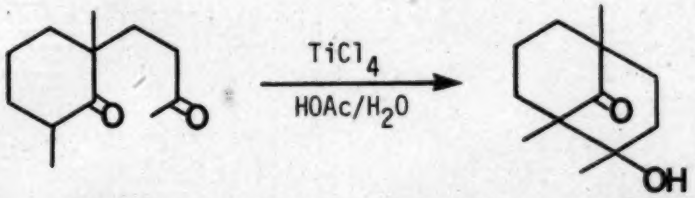


33



34

structure 33. Instead it exhibited three singlets (each containing 3 hydrogens) at δ 0.96, 1.02 and 1.23. The latter signal is characteristic of a methyl group attached to the carbon atom bearing the hydroxyl function. The product is therefore assigned as ketol 34 (eq. 32).



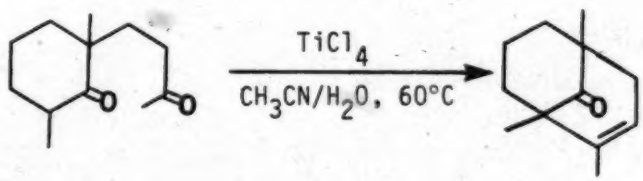
(32)

24 34

It seemed clear then that an intermediate titanium chelate of diketone 24 was not responsible for the formation of the octalone system during the hydrolysis-cyclization reaction of vinyl sulfide 30. This experiment was repeated under different reaction conditions, varying the amount of titanium tetrachloride, reaction time, solvent, and temperature. In all cases either mixtures of starting material 24, ketol 34, and dehydration product, or only 24 and 34 were obtained. However

we could not detect enone 25 in these reaction mixtures using n.m.r. and i.r. spectroscopy.

During one of these experiments when acetonitrile was used as the solvent, dehydration product 28 was obtained in 67% yield (eq. 33). The n.m.r. spectrum of

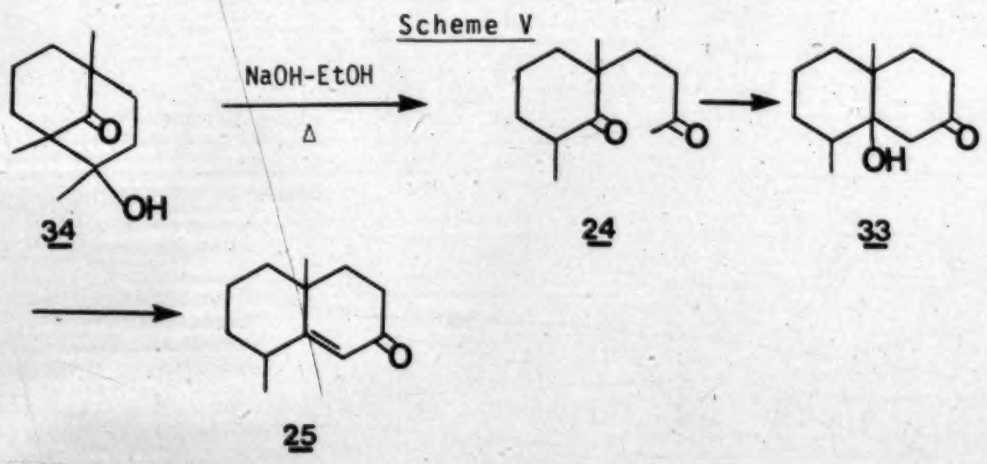


24 28 (33)

this compound proved to be identical with an authentic sample previously prepared by Dr. Benderly in this laboratory[39] (eq. 29).

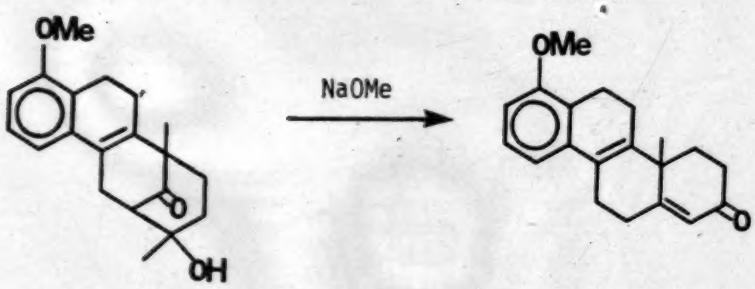
Attempts to dehydrate ketol 34 using sodium hydroxide in ethanol[47] resulted in formation of octalone 25. This suggests that the reaction involves a reverse aldol process to give diketone 24, followed by recyclization and dehydration to yield the desired octalone (Scheme V).

Scheme V



34 24 33 25

Similar observations have also been made by Johnson and co-workers,[48] and an example is shown in equation 34.



(34)

The reaction of acyclic diketones 7 and 13 with titanium tetrachloride was next investigated. Treatment of 2,6-undecanedione with $TiCl_4$ in acetic acid resulted in the formation of one major product (82%) which was identified as 2-butyl-3-methylcyclohex-2-ene-1-one 9. This reaction complements the work of Lacheveque and co-workers[4] who also showed that tetrasubstituted enone 9 is the predominant product in the mineral acid catalyzed cyclization of dione 7.

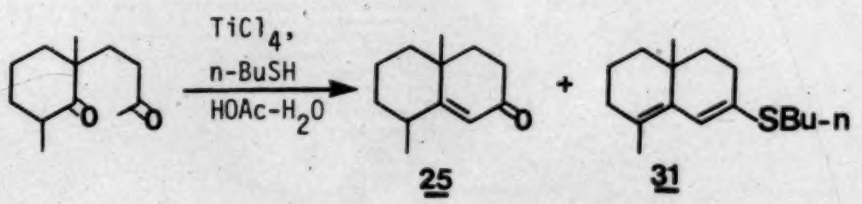
However, when 2,5-nonanedione was allowed to react with titanium tetrachloride, no cyclized products were formed, and the only isolable material was the starting diketone 13. This result also is in agreement with observations made by Hunsdiecker[6] from the reaction of 1,4-diketones with mineral acids, where no cyclized products were detected either.

It became clear at this point that "Ti chelation"

does not appear to be an important factor since the same results are obtained when acids other than $TiCl_4$ are used to catalyze the cyclization of 1,4- and 1,5-diketones.

Considering the fact that hydrolysis of vinyl sulfide 30 would liberate one mole of butanethiol, the reaction of diketone 24 with $TiCl_4$ was repeated in the presence of one equivalent of this mercaptan, in order to study the effect of the thiol produced.

Results obtained from this reaction were different from the reaction of dione 24 with $TiCl_4$ in the absence of the thiol. Glc analysis of the crude mixture indicated two major products. The infrared spectrum showed no evidence of starting material (1715, 1705 cm^{-1}), and indicated absorptions at 1590 (conjugated diene), 1680 and 1620 cm^{-1} (conjugated enone). These two products were isolated by column chromatography (silica gel, Skelly B-chloroform elution), and identified as octalone 25 (38%) and enol thioether 31 in 45% yield (eq. 35).



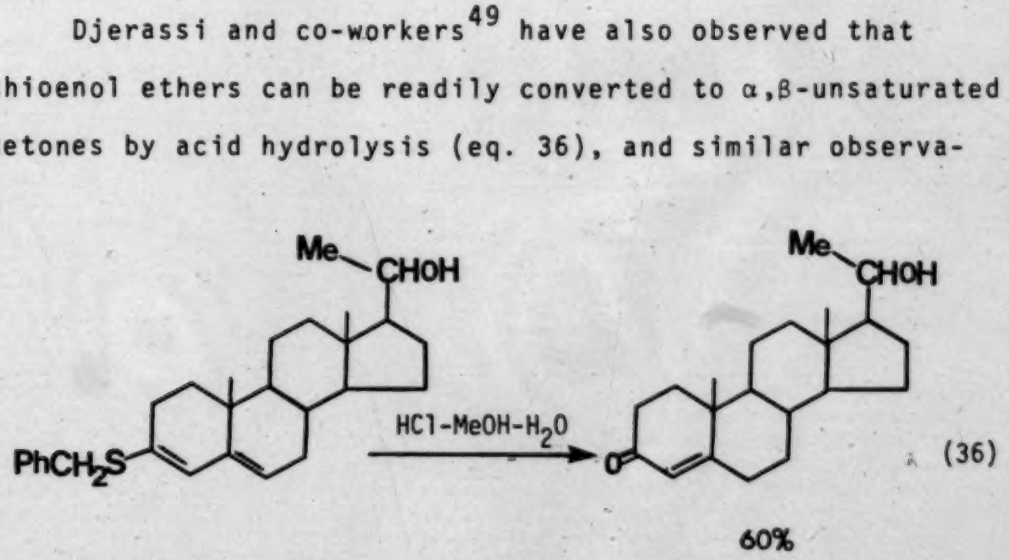
25 + 31 (35)

The n.m.r. spectrum of enone 25 was identical with that of an authentic sample prepared using Marshall's

procedure[17] (eq. 16). The structure of diene sulfide 31 was confirmed by the following spectral data: The molecular weight was determined as 250.1759 (calcd. for $C_{16}H_{26}S$: 250.1755) by high resolution mass spectroscopy; the n.m.r. spectrum (100 MHz, $CDCl_3$) exhibited signals at δ 6.3 (br, s, 1H) CH=C, 2.77 (t, 2H) CH_2-S, 2.58-1.1 (m, 17H) $(CH_2)_7$, 1.67 (s) CH_3-C=C, and 1.05-0.8 (m, 6H) methyl protons; and the i.r. spectrum showed absorption at 1590 cm^{-1} (conjugated diene).

By increasing the amount of titanium tetrachloride to 4 equiv., enone 25 became the major product, and the ratio of 25:31 increased from 0.8 to 3.8. Moreover, by monitoring the reaction course by glc analysis at time intervals of 70 min and 2 hr, it was observed that the ratio of 25:31 increased from 0.9 to 2, which indicates that diene sulfide 31 was presumably a precursor of octalone 25.

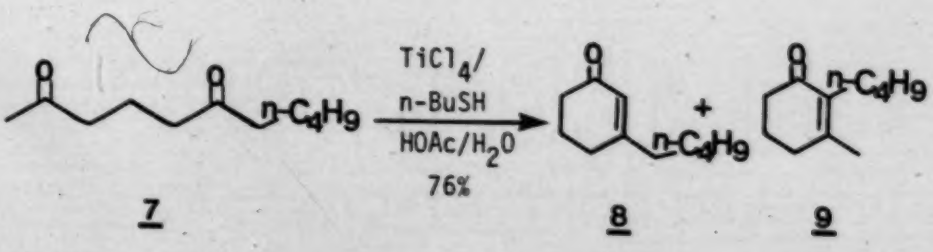
Djerassi and co-workers[49] have also observed that thioenol ethers can be readily converted to α,β-unsaturated ketones by acid hydrolysis (eq. 36), and similar observa-



(36)

tions have also been made by Dr. Benderly in this laboratory.[39] Retreatment of 31 with $TiCl_4$ in acetic acid (r.t., 1 hr) resulted in its conversion to octalone 25 in 75% yield.

In light of the interesting results observed from the reaction of dione 24 with titanium tetrachloride in the presence of the thiol, it seemed appropriate to examine the cyclization of diketones 7 and 13 under these reaction conditions. Therefore, 2,6-undecanedione was reacted with $TiCl_4$ in the presence of one equiv. of n-butanethiol. Glc analysis of the mixture indicated formation of two major products (1:1) which were separated by column chromatography and proved to be enones 8 and 9 (eq. 37).

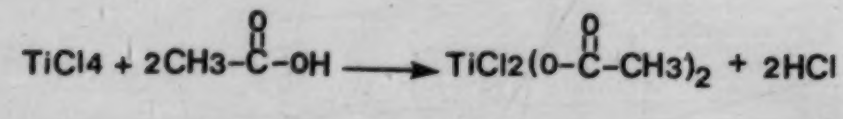


7 8 9 (37)

As is evident, the use of a thiol in the reaction of 1,5-diones with $TiCl_4$ encourages the formation of trisubstituted cycloenones to a great extent.

However, when 1,4-diketone 13 was reacted with $TiCl_4$ under these new conditions, once again it failed to cyclize and unreacted starting material was isolated from the reaction mixture.

It is known[50,51] that the reaction of titanium tetrachloride with acetic acid at room temperature produces hydrochloric acid, in addition to the diacetate of titanium (eq. 38).



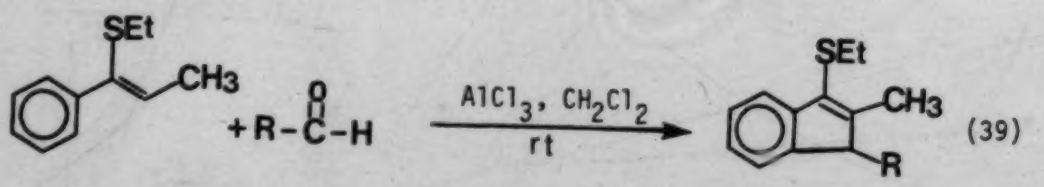
$$TiCl_4 + 2CH_3\text{-}\overset{O}{\overset{\|}{C}}\text{-}OH \longrightarrow TiCl_2(O\text{-}\overset{O}{\overset{\|}{C}}\text{-}CH_3)_2 + 2HCl \qquad (38)$$

Treatment of diketone 24 with n-butanethiol in acetic acid in the absence of $TiCl_4$ (24 h) merely resulted in the isolation of starting material, indicating the necessity of a stronger acid catalyst to promote the cyclization of the dione. However, considering the results obtained from the reaction of vinyl sulfide 30 with titanium tetrachloride (a complex mixture of products were formed) in solvents such as methylene chloride and acetonitrile, which do not react with $TiCl_4$ to produce hydrochloric acid, one could conclude that cyclization of dione 24 and vinyl sulfide 30 are most likely effected by the hydrochloric acid produced according to eq. 38. Indeed this was proven to be the case. Thus, the reaction of diketone 24 with hydrochloric acid (10 equiv.) in the presence of n-butanethiol, produced an approximately 1:1 ratio of compounds 25 and 31. These findings suggest that in spite of the reports about "$TiCl_4$ promoted reactions" in which Ti (IV) species are strongly suggested to be the responsible factor, in

solvents where formation of HCl is possible the role of this "coreagent" should also be taken into consideration.

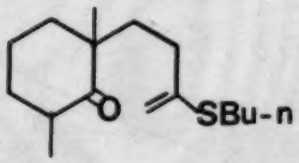
It has long been recognized that vinyl sulfides, because of the available unshared electrons on sulfur, are capable of releasing electrons in conjugative interactions with electron-deficient groups through their mesomeric ability, although this mesomeric effect was suggested to be smaller than that of the oxygen analogs.[52]

This type of electron-pair release is demonstrated by intermolecular nucleophilic attack of vinyl sulfides on carbonyl functions. For example, Mukaiyama and coworkers[53] have shown that enol thioether 35 reacts with an aldehyde in the presence of aluminum trichloride to yield vinyl sulfide 36 (eq. 39).



35 36 (39)

From this precedent, the possibility arises that enol thioether 37 could be implicated as a possible intermediate during the cyclization of compounds 30

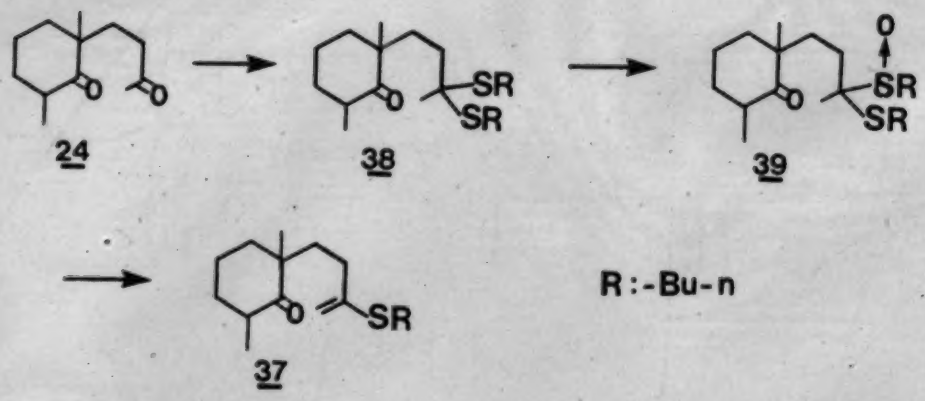


37

and 24 to yield octalone 25 and diene sulfide 31. Therefore, the preparation of ketovinyl sulfide 37 was attempted.

A conceptually simple approach to its synthesis seemed to be the utilization of dione 24 according to the route illustrated in Scheme VI.

Scheme VI

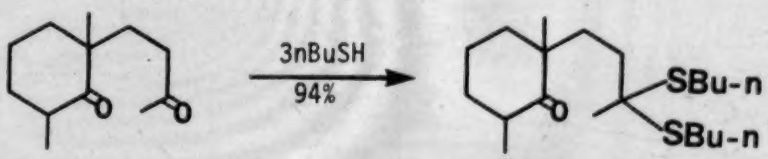


24 38 39 37

There are a number of good literature methods available for the preparation of thioketals from simple monoketones, and among them is the use of hydrochloric acid[54] as acid catalyst. However since use of hydrochloric acid resulted in the formation of cyclic products (as mentioned earlier), the use of other catalysts such as BF_3 and $ZnCl_2$ were investigated in order to stop the reaction

at the thioketalization step.

Results with boron trifluoride[55] were unpromising, since glc and ir studies indicated the formation of cyclic products. However, thioketal 38 could be prepared by a modification of a method reported by Djerassi and co-workers.[56] Thus reaction of dione 24 with n-butanethiol in the presence of zinc chloride and sodium sulfate yielded compound 38 in excellent yield (eq. 40).



38 (40)

The structure assignment was based on the following spectral data: the molecular weight was determined as 358 by chemical ionization mass spectroscopy; the ir spectrum showed carbonyl absorption at 1710 cm^{-1}; and the n.m.r. spectrum (90 MHz, $CDCl_3$) exhibited a series of signals at δ 2.8-0.8, among which were two singlets at δ 1.48 [$\underline{CH_3}$-C(SBu-n)$_2$] and 0.99 ($\underline{CH_3}$-C) and a doublet at δ 0.98 ($\underline{CH_3}$-CH).

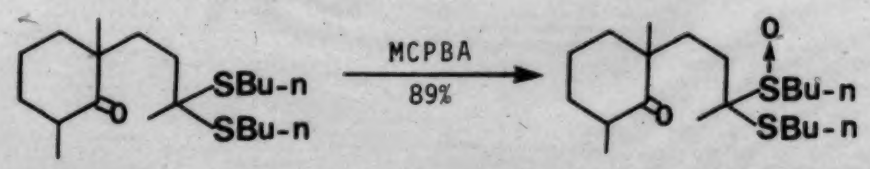
By glc mass spectral analysis, the highest peak corresponded to M^+-C_4H_9SH. This suggested the possibility that an element of n-butanethiol could be eliminated chemically without its prior conversion to the corresponding sulfoxide. However, reaction of thioketal 38

with $ZnCl_2$[54] as acid catalyst (110°C) gave no evidence for formation of 37. Only cyclic products were detected by glc, ir, and nmr analysis of the crude mixture.

Since direct conversion of thioketal 38 to vinyl sulfide 37 was unsuccessful, an attempt was made to oxidize this compound to the corresponding monosulfoxide 39, according to the original plan shown in Scheme VI.

The use of sodium metaperiodate[57,58] as oxidant led to a complex mixture of unidentified products, with no evidence of sulfoxide formation in the 1070-1030 cm^{-1} region.

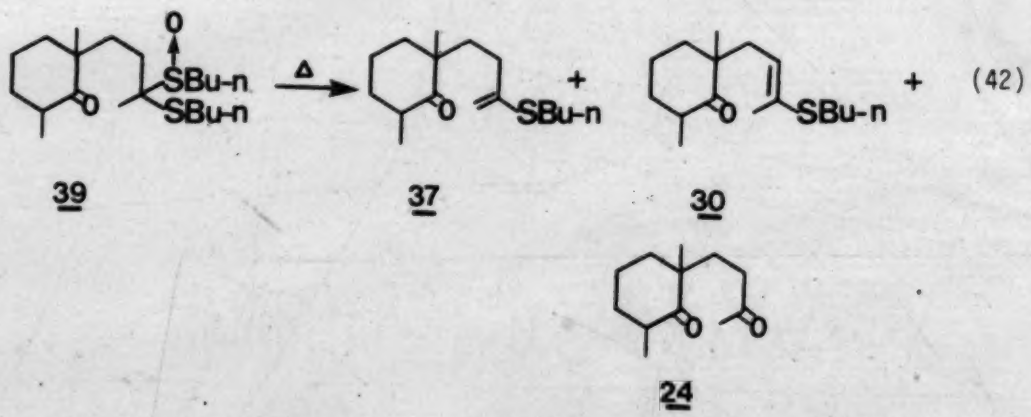
Initial results obtained from the use of m-chloroperbenzoic acid[57] (1 equiv. in methylene chloride, 0°C) were also unsatisfactory. In addition to vinyl sulfides 30 and 37, diketone 24 was also produced, presumably as a result of a hydrolysis reaction. However, when this reaction was repeated at a lower temperature (-30°C) in ether, an 89% yield of sulfoxide 39 was obtained (eq. 41). Compound 39 was readily separated from unreacted starting material (7%) by column chromatography (neutral alumina, activity III, hexane-acetone elution), and indicated ir absorptions at 1705 (C=O) and 1035 cm^{-1} (S→O).



(41)

38 39

Dehydrosulfenylation was carried out by heating a neat sample of sulfoxide 39 at 85°C, and monitoring the course of the reaction by following the disappearance of the sulfoxide absorption at 1035 cm^{-1}. The minimum time required for completion of the pyrolysis was one hour. This resulted in a mixture of enol thioethers 30 and 37 in 55% yield (1:1.8 ratio, as determined by n.m.r. spectroscopy), as well as 37% of diketone 24 (eq. 42).

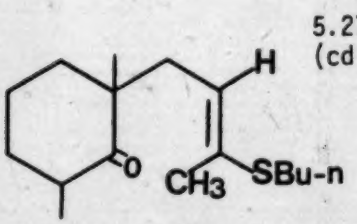


39 37 30

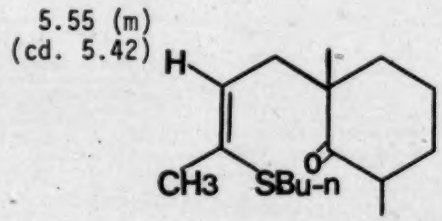
24 (42)

The isomeric vinyl sulfide mixture was separated from the diketone by column chromatography (activity III alumina, hexane elution), and the molecular weight was determined as 268.1860 (calcd. for $C_{16}H_{28}O^{32}S$: 268.1861). The ir spectrum of the mixture showed absorptions at 1705 (s) (C=O), 1630 (sh) (C=C-H), and 1605 cm^{-1} (m) ($C=CH_2$). The n.m.r. absorptions (90 MHz , $CDCl_3$) for the vinylic protons of compounds 30 (E and Z isomers 3:1 ratio) and 37 are shown below. The stereochemical assign-

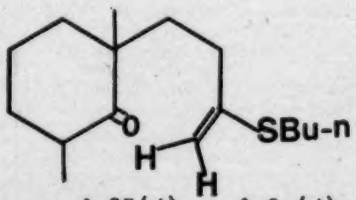
ments are based on the n.m.r. spectral correlations published earlier for olefinic protons of this type.[59]



30-(E)



30-(Z)

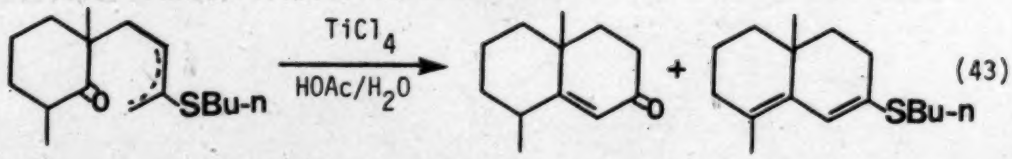


4.95(d) 4.6 (d)
(cd. 4.98) (cd. 4.75)

37

Vinyl sulfide 37 represents the thermodynamically less stable enol thioether, as reflected by the equilibration of a mixture of 30 and 37 (1:1.8 ratio) to the more substituted vinyl sulfide 30 upon standing in chloroform solution at room temperature for five days.

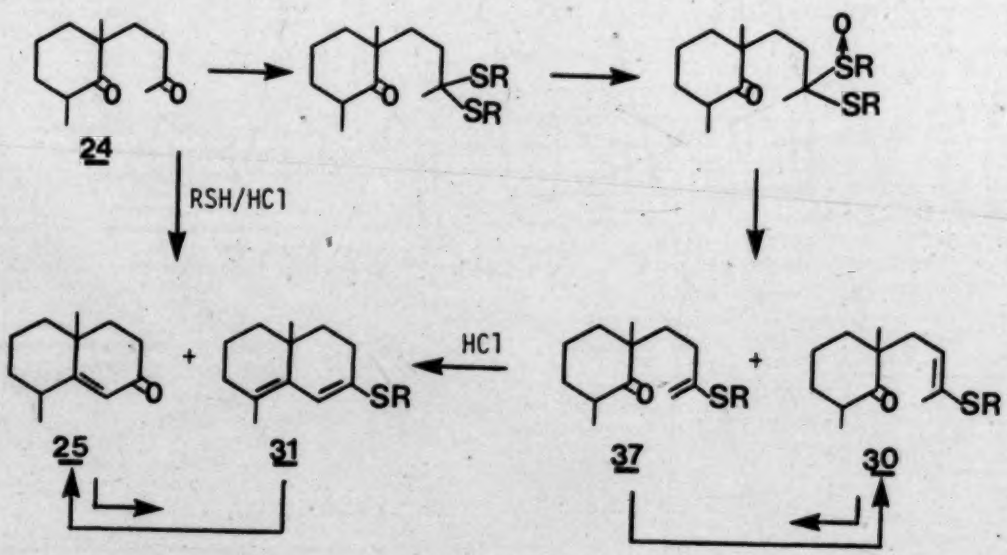
Since separation of compounds 37 and 30 was not possible, the mixture (1.8 ratio) of the two vinyl sulfides was subjected to the same cyclization conditions previously described for cyclization of compound 30. This yielded enone 25 (58%) along with 21% of the diene sulfide 31 (eq. 43).



30 & 37 25 31

Thus the formation of compounds 25 and 31 may be viewed as arising from an acid-catalyzed intramolecular aldol condensation of ketosulfide 30 and/or 37. Scheme VII presents an abbreviated summary of the preceding results.

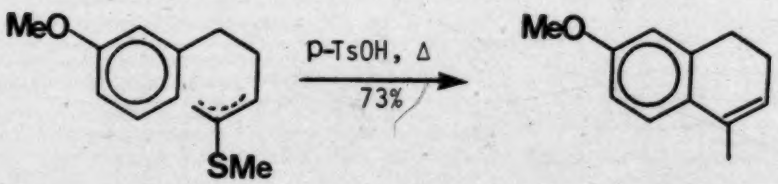
Scheme VII



According to this Scheme, no special role is attributed to the chelating abilities of titanium. Rather,

the role of $TiCl_4$ is to provide the release of HCl, thereby maintaining the proper acidity required for the cyclization reaction. This was further supported by the reaction of compound 30 (obtained from the equilibration of the mixture of 30 and 37) with hydrochloric acid in acetic acid, which produced 67% of enone 25 and 12% of diene sulfide 31.

Recently Trost and co-workers[60] have shown that enol thioethers can also act as electrophiles in cyclization reactions. For example, treatment of vinyl sulfide 40 with p-TsOH in refluxing acetonitrile produced the cyclized product 41 (eq. 44).

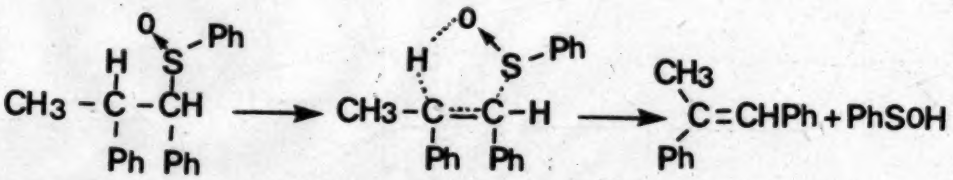


40 41 (44)

This growing interest in the field of enol thioethers and the observation made from the dehydrosulfenylation of 39 (eq. 42), suggested a more detailed examination of the pyrolysis reaction.

The thermal instability of sulfoxides has been recognized for over a century, but the exact mechanism of "decomposition" was not elucidated until 1960, when Cram and Kingsbury demonstrated that the diastereomeric

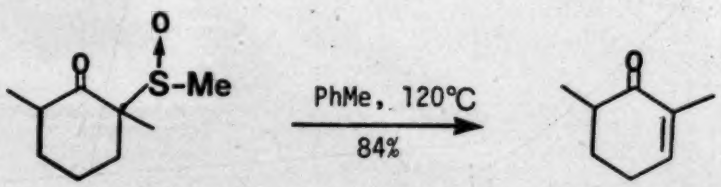
1,2-diphenyl-1-propyl phenyl sulfoxides undergo facile elimination of the elements of benzenesulfenic acid to form the isomeric α-methyl stilbenes.[61] The mechanism proposed involves a stereospecific cis-elimination as shown in equation 45.



(45)

It should be noted that lower temperatures are required for the dehydrosulfenylation reactions than needed for other olefin-forming pyrolysis reactions (i.e., amine oxides and acetates).

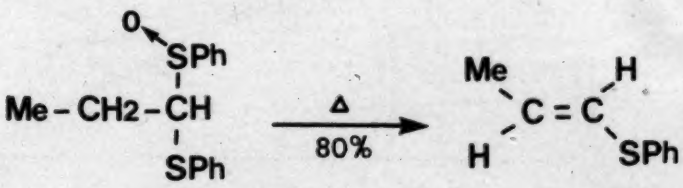
It has been shown[57] that in cases where there is the possibility of forming either of two possible regioisomers, the thermodynamically more stable product is formed predominantly, as shown in equation 46.



(46)

Another application of this reaction has been to synthesize enol thioethers. These valuable synthetic intermediates are also prepared from the elimination reaction of the corresponding thioketals,[53,62] which

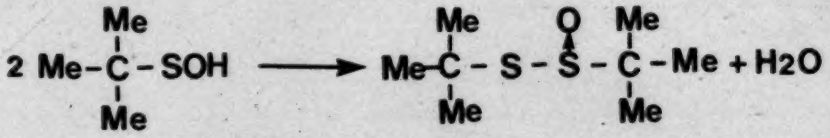
generally proceed under "thermodynamic control". On the other hand, preparation of vinyl sulfides via the dehydrosulfenylation reaction[63,64] has been limited to the use of sulfoxides derived from aldehydes, which can only produce one type of product upon pyrolysis (eq. 47). Therefore, pyrolysis of compound 39 (eq. 42) appears to



(47)

be the first example in which the dehydrosulfenylation reaction has been performed on sulfoxides derived from ketones in order to synthesize vinyl sulfides.

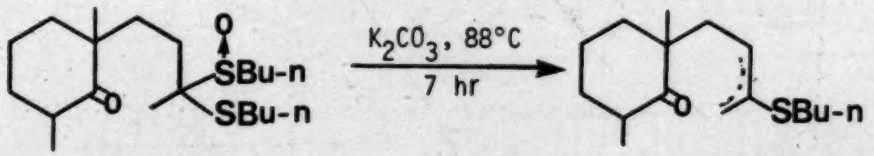
The main drawback of this reaction is formation of diketone 24, presumably as a result of hydrolysis of the starting material or the vinyl sulfide produced. It should be noted that sulfenic acid is one of the products produced during the dehydrosulfenylation. Although aliphatic sulfenic acids have not been isolated, their existence has been demonstrated by trapping[65] and other methods.[66,67] During these studies it has also been shown that sulfenic acids are labile and produce alkyl thiosulfinates as well as water[66] (eq. 48).



(48)

The production of water during dehydrosulfenylation could be one of the reasons for the observed hydrolysis product. Having this in mind, we attempted the dehydrosulfenylation in the presence of a drying agent such as potassium carbonate which at the same time could act as a base to reduce the acidity of the reaction medium.

Although a longer reaction time was required for total decomposition of the sulfoxide 39, this modification nonetheless resulted in an 87% yield of a mixture of vinyl sulfides in which the regioisomeric distribution favored the terminal isomer (terminal to internal 9:1) (eq. 49). Thus addition of potassium carbonate not only



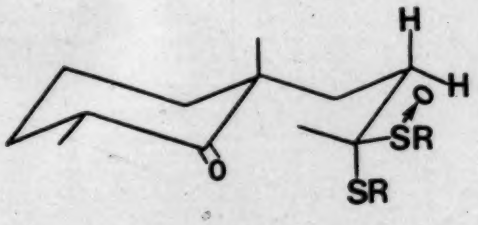
(49)

39 87%

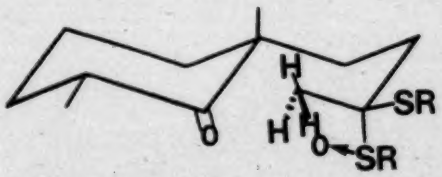
improved the yield, but the regioselectivity increased as well.

The formation of the thermodynamically less stable compound as the major product possibly could be rationalized by considering Newman projections of conformers K and L, each of which in turn lead to formation of the respective vinyl sulfides 30 and 37. As is evident, conformer L should be favored over K because of steric factors (one less non-bonded interaction than K). As

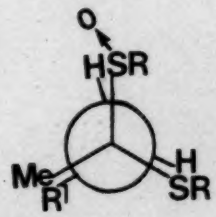
a result, the transition state leading to 30 should be of higher energy than that leading to 37.

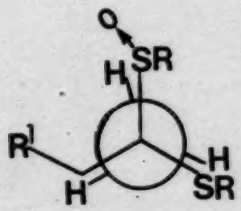


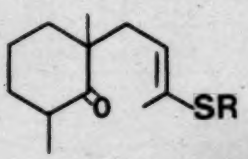
K

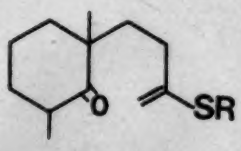


L





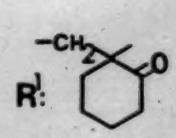




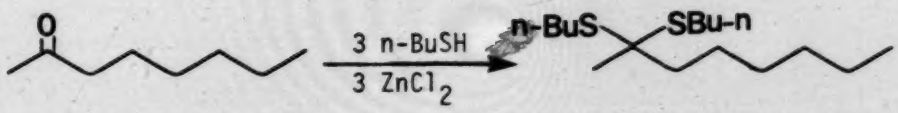
30

37

R:-Bu-n



To study this reaction further, the same scheme was selected to examine the dehydrosulfenylation of a simple acyclic unsymmetric ketone such as 2-octanone. Thus, di-n-butylthioketal 42 was prepared by reaction of n-butyl mercaptan with 2-octanone (using $ZnCl_2$) in 80% yield (eq. 50).

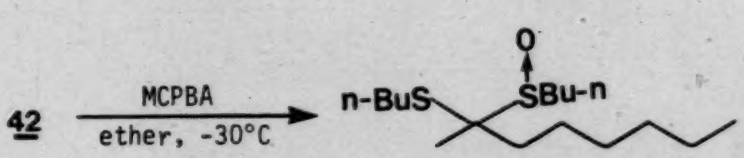


(50)

42

The n.m.r. spectrum of this compound showed signals at δ 2.58 (t, 4H) $(CH_2\text{-}S)_2$, 1.8-1.15 (m, 21H) $(CH_2)_9$, $\underline{CH_3}\text{-}C\langle^{S}_{S}$ (s, 3H at 1.47), and 1.1-0.8 (m, 9H) methyl protons, and the molecular weight was determined as 290.2099 (calcd. for $C_{16}H_{34}{}^{32}S_2$: 290.2102).

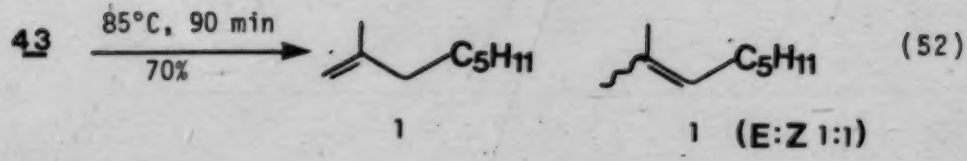
Oxidation of thioketal 42 using m-chloroperbenzoic acid[57] in ether produced the corresponding monosulfoxide 43 in 90% yield (eq. 51), whose ir spectrum exhibited the diagnostic strong sulfoxide absorption at 1035 cm^{-1}.



(51)

43

Pyrolysis of this sulfoxide was carried out under two different conditions; a) a neat sample was heated at 85°C for 90 min ; b) a sample was heated to 94°C for 5 1/2 h in the presence of potassium carbonate. The results are summarized in equations 52 and 52a.



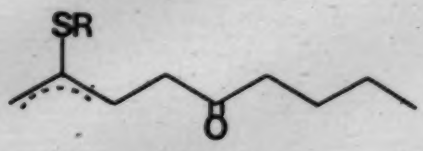
Once again, the regioselectivity and yield increased markedly using potassium carbonate.

The use of other bases such as triethylamine and N,N-diisopropylethylamine did not affect the ratio of the positional isomers, and the results were the same as equation 52, where equal amounts of the two isomers were obtained.

To the best of our knowledge this is the first instance that the dehydrosulfenylation reaction has been performed on sulfoxides derived from acyclic unsymmetrical ketones. Although mixtures of the two regioisomers are obtained, the predominant formation of the terminal enol thioether increases the potential future use of this methodology, especially, since there has been growing interest in the field of vinyl sulfides and their utilization for construction of carbon-carbon bonds.[60,68]

As a consequence of the results observed from cyclization of vinyl sulfides 30 and 37, attention was now focused on examining the directionality of the cycliza-

tion of vinyl sulfides derived from 1,4-diketones. With this in mind, preparation of vinyl sulfides of general structure 46* was investigated.

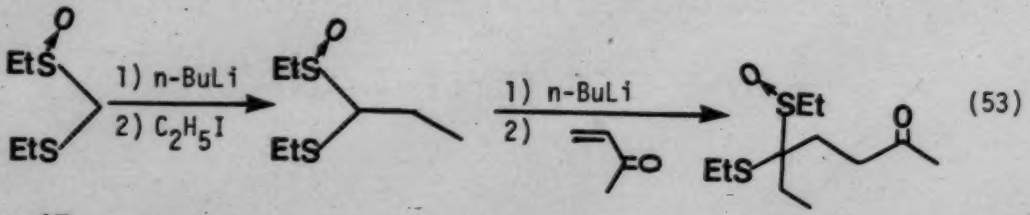


46

a: R=Me

b: R=Ph

The method of Schlessinger and co-workers[69] seemed appropriate for the synthesis of compound 46a. According to this procedure, the carbonyl anion equivalent 47 initially undergoes alkylation.[69a] Subsequent conjugate addition of the anion generated from the alkylated product to an electron defficient olefin[69b] provides the corresponding ketosulfoxide 48 (eq. 53).

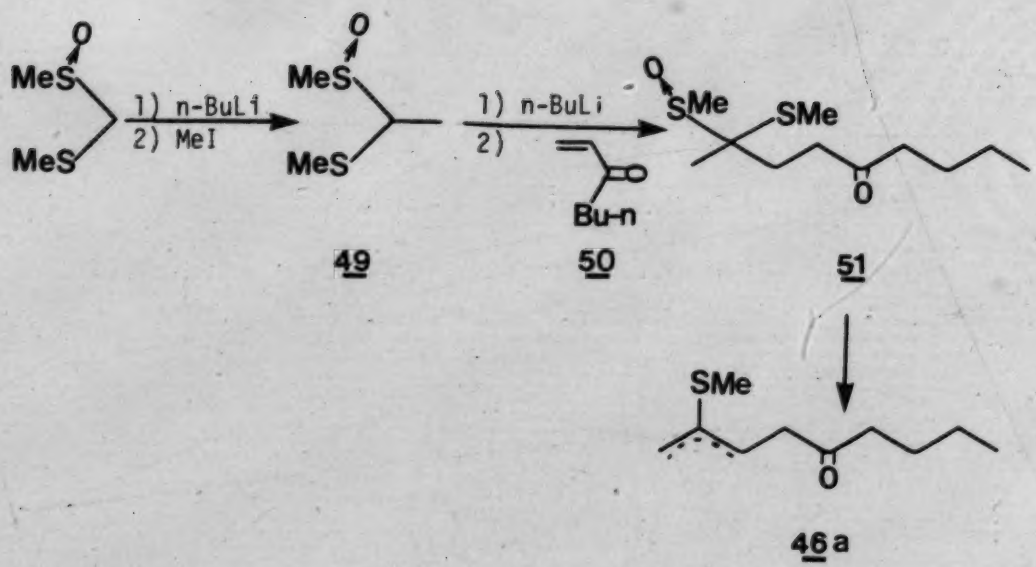


47 48 (53)

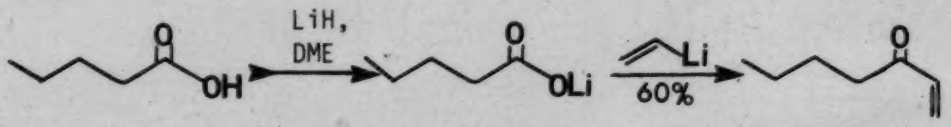
Utilizing this method compound 46a was prepared starting from methyl methylsulfinylmethyl sulfide (Scheme VIII). Preparation of n-butyl vinyl ketone 50 was made

* Since alkyl and phenyl vinyl sulfides of 1,5-diketones showed different reactivity toward hydrolysis,[39] the same analogs were prepared for 1,4-diketones.

Scheme VIII



possible through slow addition of vinyllithium to the lithium salt of Valeric acid in DME[70,71] (eq. 54).



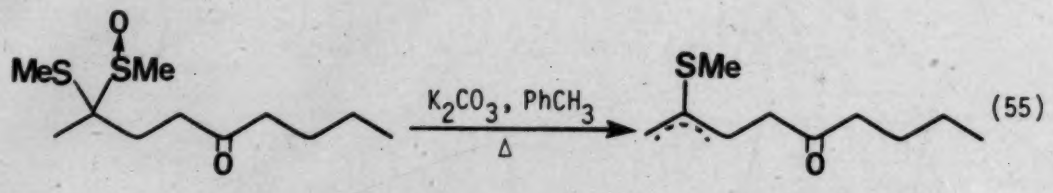
(54)

Sulfoxide 49 was obtained in 73% yield via methylation of methyl methylsulfinylmethyl sulfide using n-butyllithium and methyl iodide in THF. The structure of this compound was confirmed by the following spectral data: the ir spectrum showed sulfoxide absorption at 1050 cm^{-1}, and the n.m.r. spectrum (90 MHz, $CDCl_3$) exhibited a series of signals at δ 3.9-3.3 (m, 1H, CH), 2.62-2.5 (m, 3H, CH_3-S), 2.4-2.27 (m, 3H, CH_3-S), and

1.65 (d, 3H, $\underline{CH_3}$-CH).

Subsequent treatment of sulfoxide 49 with n-butyllithium, followed by addition of vinyl ketone 50 provided ketosulfoxide 51 in 84% yield (crude). The ir spectrum indicated strong absorptions at 1720 (>C=O) and 1050 cm^{-1} (S=O).

Ketosulfoxide 51 was subjected to the pyrolysis conditions (reflux in toluene, potassium carbonate) without purification, and the course of this reaction was monitored using ir spectroscopy. The minimum time required for complete disappearance of the sulfoxide absorption (1050 cm^{-1}) was 17 h (eq. 55).



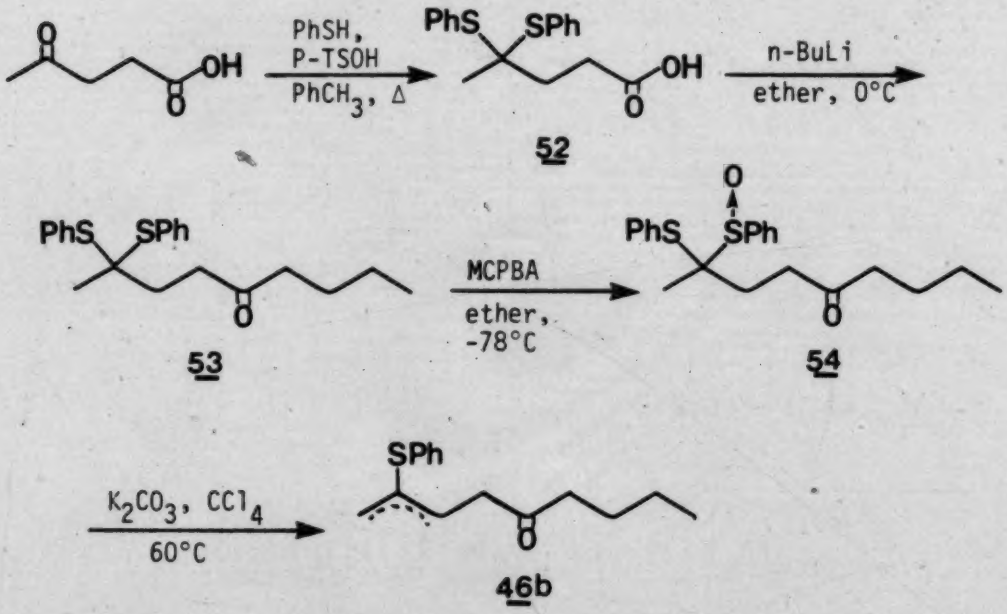
51 46a (55)

The mixture of the two regioisomers produced (terminal:internal 95:5) was separated by column chromatography on silica gel to produce 58% of compound 46a whose structure was confirmed by the following spectroscopic data: The molecular weight was determined as 186.1071 (calcd. for $C_{10}H_{18}O^{32}S$: 186.1078) by high resolution mass spectroscopy; the ir spectrum showed absorptions at 1720 cm^{-1} (C=O) and 1610 cm^{-1} (C=C); and the n.m.r.

spectrum (90 MHz, C_6D_6) exhibited signals at δ4.97 (s) SMe C=C, H 4.5 (s) H SMe C=C, 1.83 (s)-SMe.

In conjunction with the preparation of 46a, compound 46b was also prepared using a different pathway as shown in Scheme IX. Thioketal 52 was prepared from the re-

Scheme IX



action of levulinic acid and thiophenol in the presence of p-toluensulfonic acid[72] in 50% yield. High resolution mass spectroscopy indicated a molecular weight of 318.0756 (calcd. for $C_{17}H_{18}O_2{}^{32}S_2$: 318.0749); the n.m.r. spectrum (90 MHz, $CDCl_3$) showed signals at δ 11.5 (s, 1H), 7.76-7.2 (m, 10H, aromatic ring), 2.92-1.92 (m, 4H, CH_2-CH_2) and 1.33 (s, 3H, -CH_3); and the ir spectrum exhibited

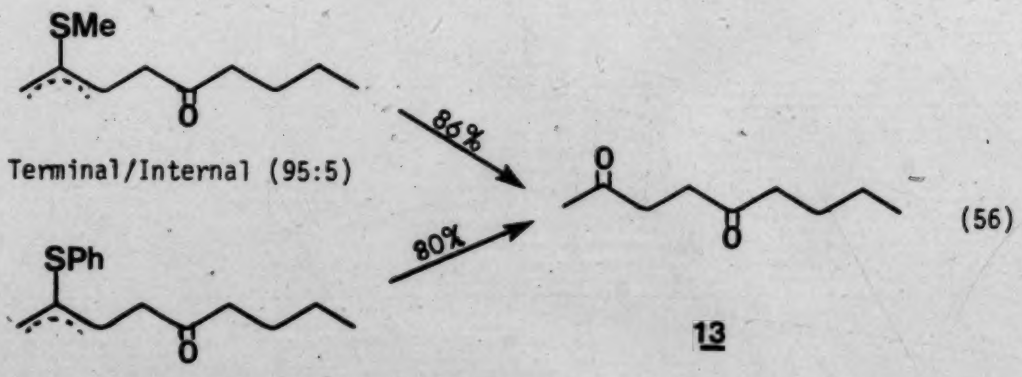
absorptions at 1715 (C=O) and 1590 cm^{-1} (C=C).

Alkylation of acid 52 using n-butyllithium in ether[70] provided 40% of the ketothioketal 53. The latter was oxidized to the corresponding ketomonosulfoxide 54 using m-chloroperbenzoic acid in ether[57]. The ir spectrum of the crude sulfoxide (91% yield) indicated absorptions at 1720 cm^{-1} (C=O) and 1050 cm^{-1} (S→O).

Dehydrosulfenylation of this product provided a mixture (1:1) of the two regioisomers of vinyl sulfide 46b in 60% yield after purification from alumina.

The n.m.r. spectrum (90 MHz CCl_4) of the mixture showed a multiplet at δ 5.92 (-$\overset{\text{SPh}}{\overset{|}{C}}$=CH) and two singlets at δ 5.13 and 4.87 (CH_2=$\overset{|}{C}$-SPh); and ir spectrum indicated absorptions at 1720 (C=O) and 1620 cm^{-1} (C=C).

Having vinyl sulfides 46a and 46b in hand, cyclization of these compounds using $TiCl_4$ in acetic acid was attempted. However, this merely resulted in the hydrolysis of both compounds to yield 2,5 nonanedione (eq. 56).



(56)

No cyclization products could be detected by glc, n.m.r. and ir analysis of the mixture obtained, and 1,4-diketone 13 was the only product detected and isolated from these reactions.

The failure to obtain cyclopentenones from the reaction of vinyl sulfides derived from acyclic 1,4-diketones with acid stands in marked contrast to the results observed from the reaction of compounds 30 and 37 with acid, where octalone systems were obtained as the major products.

In light of the observations made by Lacheveque and co-workers[4] from the reaction of several 1,5-diketones with lithium diisopropylamide (eq. 3), the possibility arose that the analogous cyclization of 1,4-diketone 13 may be effected using this method. Therefore 2,5-nonanedione was allowed to react with LDA in ether at -65°C. After work up, glc analysis of the mixture showed the presence of starting material and several other products having higher retention times than starting diketone. However no cyclized products could be detected in the product mixture. Diketone 13 was separated from the more polar components of the mixture by column chromatography on silica gel (50%). Elution of the polar compounds followed by glc mass spectral analysis indicated the presence of dimeric products. Variation of the reaction conditions, such as temperature and reaction time, did

not change the course of this reaction. The use of high dilution resulted in the formation of fewer dimeric products, but nevertheless, no cyclized products could be detected as a result of this variation.

Whether or not cyclization is in fact taking place during this reaction, but under the reaction conditions employed, is reversible (and undergoes reverse aldol) to give the original diketone is not known.

In conclusion, this investigation has led to a further understanding of the processes involved in the conversion of 2-[γ-phenyl(n-butyl)thio crotyl] cyclohexanone derivatives to the corresponding octalone systems, using titanium tetrachloride in acetic acid. It was shown that "Ti chelation" does not appear to be important, and the role of $TiCl_4$ is most likely to provide the hydrochloric acid needed for the intramolecular condensation of these ketovinyl sulfides. Since this methodology involved specific generation of the enol equivalent at the desired site of dicarbonyl compounds, its possible application to 1,4-diketones was investigated. It was shown that vinyl sulfides derived from 1,4-diketones fail to cyclize, and instead they hydrolyze to yield the corresponding diketones.

In pursuing this line of study, a direct comparison was made between the cyclization of acyclic 1,4- and 1,5-diketones, under several different reaction conditions.

These studies have demonstrated very clearly the dramatic differences between the construction of 5- and 6-membered rings. For example, attempted cyclization of 1,4-diketone 13 under basic and acidic conditions failed to yield any cyclized products, whereas, mixtures of cyclohexenones were obtained from the reaction of 1,5-diketone 7 under similar reaction conditions.

EXPERIMENTAL

General Consideration

Infrared (ir) spectra were recorded using an Unicam SP-1000 Infrared Spectrophotometer. The following abbreviations are used: s = strong, m = medium, w = weak, and sh = shoulder.

Nuclear magnetic resonance (nmr) spectra were run on a Varian A-60, Perkin-Elmer R-32 at 90 MHz, or, Varian HA-100 Spectrometer. Chemical shifts are reported as δ values in part per million downfield from tetramethylsilane. The following abbreviations were used in the text: s = singlet, d = doublet, t = triplet, and m = multiplet.

Mass spectra were recorded on an AEI Model MS-2, MS-12, and MS-9 mass spectrometer (chemical ionization). Exact mass measurements were performed on an AEI Model MS-50 spectrometer, and are reported as m/e (relative intensity).

Gas liquid chromatography (glc) was performed using Varian Aerograph Series 1200 and 1400 instruments. The following columns were used: column A: 10'/1/8" 15% SE-30 on chromosorb G-DMCS; column B: 10'/1/8" 10% Carbowax 20 M on chromosorb W.

The concentration of commercial n-butyllithium in hexane was determined by titration using diphenyl

acetic acid.[73] Reagents and solvents were purified according to established procedures.[74]

Preparation of 2-methyl-6-n-pentylpyridine. A dry three-necked flask (300 ml) equipped with addition funnel, a magnetic stirring bar, and N_2 inlet was charged with a solution of n-butyllithium (50 ml, 2.36 M, 0.118 mol) in hexane. To this, a solution of 12.5 g (0.117 mol) of 2,6-lutidine in 25 ml anhydrous ether was added dropwise. The mixture was stirred at reflux for 30 min, and then 8.015 g (0.0585 mol) of n-butyl bromide in 6 ml of anhydrous ether was added. The solution was heated under reflux for 30 min, this was followed by dilution with water and extraction with ether. The organic layers were combined and dried (Na_2SO_4). Evaporation of the solvent afforded 15 g of a yellow oil. Vacuum distillation of the crude oil yielded 4.4 g of lutidine: bp 53-54°C (19 mm Hg), and 6.3 g (66%) of 2-methyl-6-n-pentylpyridine as a pale yellow liquid: bp 84°C (3 mm Hg); ir (liquid film): 1600, 1585, 1465 cm^{-1}; nmr (90 MHz, $CDCl_3$): δ 7.55-7.3 (m, 1H), 7-6.8 (m, 2H), 2.73 (t, 2H) $\underline{CH_2}$-C=N-, 2.46 (s, 3H) $\underline{CH_3}$-C=N-, 1.9-1.15 (m, 6H) $(CH_2)_3$, 0.88 (t, 3H) $\underline{CH_3}$.

Preparation of 2,6-undecanedione 7. To a solution of 2.00 g (12.2 mmol) of 2-methyl-6-n-pentylpyridine in 2.226g (2.9 ml, 48.8 mmol) of absolute ethanol and 12 ml

of anhydrous ether in 120 ml of anhydrous liquid ammonia (freshly distilled from sodium), was slowly added 0.464 g (28 mmol) of sodium metal. The solution was stirred for 20 min and the volatiles were evaporated under a stream of nitrogen. To the residue was added 20 ml of 10% H_2SO_4 and the solution was stirred at room temperature for 20 min. The reaction mixture was diluted with 20 ml of water and extracted with three 100 ml portions of ether. The organic layers were dried over anhydrous Na_2SO_4, and the solvent was removed to afford 1.5 g (65%) of diketone 7 as tan crystals: mp 45-47°C; ir ($CHCl_3$) 1720 cm^{-1} (C=O); nmr (90 MHz, $CDCl_3$): δ 2.65-2.25 (m, 6H) $(CH_2-\overset{O}{\overset{\|}{C}}-)_3$, 2.1 (s, 3H) $\underline{CH_3}-\overset{O}{\overset{\|}{C}}-$, 2-1.1 (m, 8H) $(CH_2)_4$, 0.88 (t, 3H) $\underline{CH_3}-CH_2$.

Preparation of 2-methyl-5-n-butylfuran 32. A dry three-necked flask (100 ml) equipped with thermometer, addition funnel, a magnetic stirring bar, and N_2 inlet was charged with a solution of n-butyllithium (32 ml, 1.57 M, 50 mmol) in hexane, and 10 ml of THF. The solution was cooled to -25°C and 2-methylfuran (4.1 g, 50 mmol) dissolved in 10 ml of THF was added over a period of 30 min; stirring was then continued for 4 hr at -15°. After this period, a solution of n-butyl bromide (6.85 g, 50 mmol) in 10 ml of THF was added dropwise and with stirring over 20 min. The reaction mixture was stirred for an additional hour at -15°; then the cooling bath was re-

moved, and the mixture was allowed to stir overnight. It was poured over crushed ice and the two layers were separated. The aqueous layer was extracted with ether, and the combined organic layers were washed with brine, dried over Na_2SO_4 and evaporated to yield a yellow liquid. Vacuum distillation gave 4.9 g (70%) of compound 32 as a colorless liquid bp 61-63°C (23 mm Hg); ir (liquid film): 1570 cm^{-1}; nmr (60 MHz, CCl_4): δ 5.7 (s, 2H) $(-\underline{CH}=C)_2$, 2.52 (t, 2H) $\underline{CH_2}-C=C$, 2.17 (s, 3H) $\underline{CH_3}-C=C$, 1.7-1.1 (m, 4H) $(CH_2)_2$, 0.95 (t, 3H) $\underline{CH_3}$.

Preparation of 2,5-nonanedione 13. Glacial acetic acid (2 ml), water (0.5 ml), 20% H_2SO_4 (0.14 ml), and 2.326 g (17 mmol) of 2-methyl-5-n-butylfuran were combined and heated at 120° for 3 hr. The resulting red solution was cooled and poured into water, extracted with pentane, washed with saturated $NaHCO_3$ solution, and dried over Na_2SO_4. Solvent evaporation afforded 2.41 g of a crude product which was distilled to yield 2.1 g (80%) of the desired diketone 13: bp 80-82°C (2.5 mm Hg); ir: (liquid film) 1715 cm^{-1} (C=O); nmr (90 MHz, $CDCl_3$): δ 2.66 (s, 4H) $-\overset{O}{\overset{\|}{C}}-\underline{CH_2}-\underline{CH_2}-\overset{O}{\overset{\|}{C}}-$, 2.45 (t, 2H) $\overset{O}{\overset{\|}{C}}-\underline{CH_2}-CH_2$, 2.13 (s, 3H) $\underline{CH_3}-C=O$, 1.75-1.1 (m, 4H) $(CH_2)_2$, 0.98 (t, 3H) $\underline{CH_3}$.

Preparation of 2,6-dimethyl-2-(3-oxobutyl)cyclohexanone. To a 100 ml flask equipped with a magnetic stirring bar

and a drying tube was added 9.5 g (10.3 ml, 75 mmol) of 2,6-dimethylcyclohexanone, 5.25 g (6.1 ml, 75 mmol) of freshly distilled methyl vinyl ketone, and 50 ml benzene. The mixture was cooled to 0°C and stirred while 1.5 ml of concentrated sulfuric acid was added. Then the mixture was allowed to stand at 0°C for 2 hr. The orange mixture was then stirred and a second portion of methyl vinyl ketone 2.6 g (3.0 ml, 37.5 mmol), and sulfuric acid (0.5 ml) was added. After standing for an additional 2 h, final portions of methyl vinyl ketone (3.0 ml) and sulfuric acid (0.5 ml) were mixed with the dark reaction mixture. After standing for 12 hr at 0°C, the orange reaction mixture was decanted from the dark polymer and poured into 100 ml of ether. The polymer was rinsed with 50 ml of fresh ether, the combined ethereal solutions were washed with 1 N sodium hydroxide solution and then brine. The aqueous washings were back-extracted with ether. The organic extracts were combined, washed with water, and dried ($MgSO_4$) and the solvents were removed at reduced pressure to give an orange oil (14.0 g). Chromatography over silica gel (200 mesh) using chloroform-Skelly B (2:3) as eluting solvent gave 5.9 g (40%) of compound 24: bp 85-95°C (0.7 mm Hg) (lit,[17] 82-100/0.2 mm); ir (liquid film): 1715 and 1705 cm^{-1} (C=O); nmr (90 MHz, $CDCl_3$): δ 2.13 (s, 3H) $\underline{CH_3}$-C=O, 0.97 (s, 3H) $\underline{CH_3}$-C, 0.96 (d, J = 6.5 Hz,

3H) $\underline{CH_3}$-CH; mass spectrum m/e: 196.1466 (calcd. for $C_{12}H_{20}O_2$: 196.1463).

Reaction of 2,6-dimethyl-2-(3-oxobutyl)cyclohexanone with titanium tetrachloride in acetic acid. A dry three-necked flask (100 ml) equipped with thermometer, addition funnel, condenser, and a magnetic stirring bar was charged with glacial acetic acid (24 ml). Titanium tetrachloride (0.78 ml, 7.2 mmol) was added which caused the solution to turn yellow immediately, and the temperature rose to 35°C. After 3 min at room temperature a white precipitate resulted. This mixture was stirred at room temperature for an additional 3 min, then a solution of 2,6-dimethyl-2-(3-oxobutyl)cyclohexanone 24 (0.588 g, 3 mmol) in glacial acetic acid (6 ml) was added. The resulting red solution was stirred for 20 min at room temperature. At the end of this period water (0.216 g, 12 mmol) was added (which immediately caused the precipitate to dissolve) and the mixture was stirred for 4 hr. The reaction mixture was poured into a cold saturated solution of potassium carbonate (100 ml), extracted with ether (3 x 50 ml), and dried ($MgSO_4$). After removal of the solvent, 0.54 g of a light yellow viscous liquid was obtained which was chromatographed over silica gel (200 mesh) using chloroform-Skelly B (1:1) as eluting solvent to give 0.05 g of the starting diketone (8%), and 0.46 g (79%) of 1,2,5-trimethyl-

bicyclo-[3.3.1]non-2-ol-9-one, 34, as a light yellow liquid: ir (liquid film) 3510(OH), 1710 cm^{-1} (C=O); nmr (90 MHz, $CDCl_3$): δ 2.3-1.3 (m, 11H) $(\underline{CH_2})_5$,OH, 1.23 (s, 3H) $\underline{CH_3}$-C-OH, 1.02 (s, 3H) $\underline{CH_3}$-C, 0.96 (s, 3H) $\underline{CH_3}$-C; mass spectrum m/e: 196.1455 (calcd. for $C_{12}H_{20}O_2$: 196.1463), 196(11), 178(1), 125(100), 107(9), 95(9), 81(16), 69(9), 55(21), 53(10).

Reaction of 2,6-dimethyl-2-(3-oxobutyl)cyclohexanone with titanium tetrachloride in acetonitrile. Acetonitrile (30 ml) and 2 ml (18 mmol) of titanium tetrachloride were added to a three-necked flask (100 ml) equipped with thermometer, addition funnel, condenser, and a magnetic stirring bar. After 6 min at room temperature, a solution of 0.784 g (4 mmol) of diketone 24 dissolved in acetonitrile (8 ml) was added and the mixture was stirred for an additional 20 min at room temperature. Water (0.288 g, 16 mmol) was added, and the dark red solution was heated at 60°C for 4 hr. After this period it was diluted with ether (100 ml), filtered through celite, washed wtih 5% solution of sodium bicarbonate, then brine and finally dried ($MgSO_4$) and evaporated to give 0.65 g of a yellow oil. A pure sample of 1,2,5-trimethyl-bicyclo[3.3.1]non-2-en-9-one 28 (0.48 g, 67%) was obtained by bulb-to-bulb distillation: bp 65-70°C (0.8 mm Hg); ir (liquid film): 1715 cm^{-1} (C=O); nmr (90 MHz, $CDCl_3$): δ 5.57 (m, 1H) $\underline{HC}$=C, 2.4-2.2 (m, 2H) $\underline{CH_2}$-C=C,

2-1.2 (m, 9H) $(CH_2)_3$, $\underline{CH_3}$-C=C (at 1.6) 1.04, 0.97 (s, 6H) $(CH_3)_2$; mass spectrum m/e: 178(100), 177(23), 163 (24), 125(17), 110(9).

Reaction of 2,6-undecanedione with titanium tetrachloride.

Titanium tetrachloride (0.26 ml, 2.4 mmol) was dissolved in 7.6 ml of glacial acetic acid and after 6 min at room temperature, diketone 7 (0.184 g, 1 mmol) dissolved in 2 ml of glacial acetic acid was added. The mixture was stirred for an additional 20 min, and then 0.072 ml (4 mmol) of water was added. After 4 hr at room temperature it was poured into a cold saturated solution of potassium carbonate (30 ml), extracted with ether, and dried ($MgSO_4$). Removal of the solvent afforded 0.15 g a yellow liquid. Column chromatography over silica gel (200 mesh) using benzene-ether (1:1) as eluting solvent gave 0.132 g (82%) of 2-butyl-3-methylcyclohex-2-en-1-one 9; ir (liquid film) 1675, 1635 cm^{-1} (conjugated enone); nmr (90 MHz, $CDCl_3$): δ 2.5-1.8 (m, 9H), 1.9 (s), 1.6-0.8 (m, 9H), mass spectrum m/e 166.1360 (calcd. for $C_{11}H_{18}O$ 166.1358).

Reaction of 2,5-nonanedione with titanium tetrachloride.

Using the same procedure as above, compound 13 (0.468 g, 3 mmol) was treated with titanium tetrachloride (0.82 ml, 7.2 mmol) in glacial acetic acid (20 ml), and water (0.216 ml, 12 mmol). The reaction mixture was stirred

for 4 hr at room temperature. After usual workup, glc analysis (column B, 150°C) indicated only the presence of starting material (85%).

Reaction of 2,6-dimethyl-2-(3-oxobutyl)cyclohexanone with titanium tetrachloride in the presence of 1-butanethiol.

Titanium tetrachloride (0.78 ml, 7.2 mmol) was added to 24 ml of glacial acetic acid and the resulting yellow mixture was stirred at room temperature for 5 min. Then 1-butanethiol (0.36 ml, d = 0.842, 3 mmol) was added, and the mixture was stirred for an 8 additional min, then 2,6-dimethyl-2-(3-oxobutyl)cyclohexanone (0.588 g, 3 mmol) in 6 ml of glacial acetic acid was added. The resulting brown solution was stirred for 20 min prior to the addition of 0.21 g (12 mmol) of water. This reaction mixture was stirred at room temperature for 4 hr, and then quenched with a cold saturated solution of potassium carbonate (100 ml), extracted with ether, washed with sodium hydroxide solution (4 N), water, brine, and dried over $MgSO_4$. Evaporation of the ethereal solution resulted in the isolation of 0.7 g of a yellow oil. Column chromatography over silica gel (200 mesh, hexane-chloroform 1:1 as eluent) gave in order of elution: vinyl sulfide 31, [0.34 g (45%), ir (liquid film): 1590 cm^{-1} (conjugated double bond); nmr (100 MHz, $CDCl_3$): δ 6.3 (b, s, 1H) CH=C, 2.9-2.63 (t, 2H) CH_2-S-, 2.58-1.1

(m, 17H) $(CH_2)_7$, $\underline{CH_3}$-C=C (as a singlet at 1.67), 1.05-0.8 (m, 6H) methyl protons; mass spectrum m/e: 250.1759 (calcd. for $C_{16}H_{26}{}^{32}S$: 250.1755), 250(100), 235(33), 161 (50), 145(9), 105(13)]; and then, enone 25 (0.20 g, 38%) which had identical nmr and ir spectra with the authentic sample prepared according to Marshall's procedure.[17]

Preparation of 8,10-dimethyl-1(9)-octal-2-one. A solution containing 0.225 g (1.14 mmol) of 2,6-dimethyl-2-(3-oxobutyl)cyclohexanone and sodium ethoxide [generated from 0.03 g (1.3 mmol) sodium, and 6 ml of ethanol] was heated at 50°C for 1 hr. The cooled solution was poured into water and the product was extracted with ether (3 x 15 ml). The organic extract was washed with brine, dried (Na_2SO_4), and concentrated (rotary evaporator) to afford a yellow oil (0.20 g). This compound was purified by bulb-to-bulb distillation, 100°C/0.4 mm, to give 0.18 g (88%) of compound 25, ir (liquid film): 1680 (conjugated carbonyl group), and 1614 cm^{-1} (conjugated double bond); nmr (90 MHz, $CDCl_3$): δ 5.75 (d, J = 2, 1H) $\underline{CH}$=C, 2.5-1.3 (m, 11H) $(CH_2)_5$, -$\underline{CH}$-CH_3, 1.25 (s, 3H) $\underline{CH_3}$, 1.05 (d, J = 6.5 Hz, 3H) $\underline{CH_3}$-CH; mass spectrum m/e: 178.1358 (calcd. for $C_{12}H_{18}O$: 178.1358).

Reaction of 2,6-undecanedione with $TiCl_4$ in the presence of n-butylmercaptan. To a mixture of titanium tetrachloride (0.26 ml, 2.4 mmol) and n-butanethiol (0.11 ml,

1 mmol) in 8 ml of glacial acetic acid at room temperature was added 0.184 g (1 mmol) of diketone 7 dissolved in 2 ml of glacial acetic acid, which caused an immediate color change from yellow to purple and then red. After 20 min at room temperature, water (0.72 ml, 4 mmol) was added and the mixture was stirred at room temperature for an additional 4 hr. Work up as before followed by chromatography over silica gel (200 mesh, benzene-ether 1:1 as eluent) gave in order of elution: compound 9, which had identical nmr and ir spectra to the compound isolated previously, and 3-pentylcyclohex-2-en-1-one 8, [0.064 g (38%), ir (liquid film): 1680, 1630 cm^{-1} (conjugated enone); nmr (90 MHz, $CDCl_3$): δ 5.87 (sharp triplet, 1H), 2.5-1.2 (m, 14H) $(CH_2)_7$, 0.89 (t, 3H) CH_3; mass spectrum m/e 166.1360 (calcd. for $C_{11}H_{18}O$: 166.1358).

Reaction of 2,5-nonanedione with $TiCl_4$ and 1-butanethiol.

Using the same procedure as above, compound 13 (0.468 g, 3 mmol) was treated with 1-butanethiol (0.33 ml, 3 mmol), and titanium tetrachloride (0.82 ml, 3 mmol) in glacial acetic acid (20 ml) and water (0.216 ml, 12 mmol). The reaction mixture was stirred for 4 hr at room temperature. After usual work up, glc analysis (column B, 150°) indicated only the presence of starting material. Column chromatography over silica gel yielded 0.375 g (80%)

of the diketone 13.

Reaction of 2,6-dimethyl-2-(3-oxobutyl)cyclohexanone with n-butanethiol in acetic acid. Diketone 24 (0.245 g, 1.25 mmol) was dissolved in 8 ml of glacial acetic acid. To this solution, 0.13 ml (1.25 mmol) n-butanethiol was added, and the reaction mixture was stirred at room temperature for 28 hr. After this period, it was poured into 50 ml of cold saturated solution of potassium carbonate, extracted with ether, washed with sodium hydroxide (4 N), brine, and dried over Na_2SO_4. After evaporation of the solvent, 0.23 g (95%) of starting diketone was recovered.

Reaction of diketone 24 with hydrochloric acid in the presence of n-butanethiol. To a solution containing hydrochloric acid [generated from the reaction of 0.36 ml (20 mmol) of water with 1.42 ml (20 mmol) acetyl chloride] in 18 ml acetic acid was added 0.234 ml (2 mmol) of n-butanethiol. The mixture was stirred at room temperature for 2 min, then 0.392 g (2 mmol) of 2,6-dimethyl-2-(3-oxobutyl)cyclohexanone, dissolved in 2 ml of glacial acetic acid, was added. This caused the solution to turn orange-red immediately, and then dark brown. After stirring at room temperature for 90 min, it was quenched with a cold saturated solution of potassium carbonate (50 ml), extracted wtih ether, washed with

sodium hydroxide (4 N), brine, and dried ($MgSO_4$). Evaporation gave 0.45 g of yellow oil which was chromatographed from silica gel to give 0.247 g (46%) of vinyl sulfide 31, and 0.145 g (40%) of enone 25. Both had identical nmr and ir spectra with compounds isolated earlier.

Reaction of the diketone 24 with boron trifluoride etherate in the presence of 1-butanethiol. A solution of 0.196 g (1 mmol) of 2,6-dimethyl-2-(3-oxobutyl)-cyclohexanone in 0.46 ml (4.3 mmol) of n-butyl mercaptan and 0.36 ml of boron trifluoride etherate was allowed to stand at room temperature for 10 min. After addition of 5 ml of chloroform to the dark orange reaction mixture it was allowed to stand overnight at room temperature. The resultant dark brown solution was diluted with 50 ml of chloroform, washed with sodium hydroxide solution, brine, and dried (Na_2SO_4). Solvent was evaporated at reduced pressure to provide 0.26 g of yellow oil. Glc analysis (column A, 170°) indicated the formation of diene sulfide 31 (70%) and 8,10-dimethyl-1(9)-octal-2-one (18%).

Synthesis of the thioketal 38. A 100 ml flask equipped with a magnetic stirring bar and a drying tube was charged with 1.96 g (10 mmol) of diketone 24, dioxane (10 ml), and 3.24 ml (30 mmol) of n-butyl mercaptan. The mixture

was cooled (ice bath) and 4 g (30 mmol) of freshly fused zinc chloride and 4 g of anhydrous sodium sulfate was added. The resulting mixture was stirred at room temperature for 3 hr. Then 50 ml of water was added, the mixture was extracted with chloroform (3 x 20 ml), washed with sodium hydroxide solution (4 N), brine, and dried ($MgSO_4$). After evaporation of the solvent under reduced pressure, 3.5 g of a pale yellow oil was obtained. TLC (silica gel) indicated only one spot, this was further purified by passing through a short alumina column (act III, hexane eluent). In this way 3.35 g (94%) of thioketal 38 was obtained, ir (liquid film): 1710 cm^{-1} (C=O); nmr (90 MHz, $CDCl_3$): δ 2.8-2.4 (m, 5H) ($\underline{CH_2}$-S)$_2$, $\underline{CH}$-C=O, 2.2-1.2 (m, 21H) $(CH_2)_9$, $\underline{CH_3}$-C(S)(S) (s, 1.48), 1.1-0.8 (m, 12H) $(CH_3)_4$; the chemical ionization (NH_3) mass spectrum showed the $M^+ + 18$ (m/e 376 peak); mass spectrum $M^+ - C_4H_9S$: 269.1945 (calcd. for $C_{16}H_{29}O^{32}S$: 269.1939).

Pyrolysis of thioketal 38 in the presence of zinc chloride. Thioketal 38 (0.18 g, 0.5 mmol), and 0.05 g (0.4 mmol) of freshly fused zinc chloride were heated at 110°C for 30 min. The dark green solution was then dissolved in ether, washed with brine, and dried ($MgSO_4$). Evaporation gave 0.15 g of an orange oil. Glc analysis (column A, 170°) indicated the formation of the diene

sulfide 31 (major product) and the enone 25.

Reaction of thioketal 38 with sodium metaperiodate. To 2.1 ml (1.05 mmol) of a 0.5 M solution of sodium metaperiodate at 0°C was added 0.358 g (1 mmol) of thioketal 38 in 3 ml of methanol. The ice bath was removed and the reaction was stirred at room temperature for 1 hr. The precipitate of sodium iodate was removed by filtration, and the filtrate was extracted with chloroform. The extract was dried ($MgSO_4$), and the solvent was removed under reduced pressure. The ir spectrum of the product(s) lacked the sulfoxide absorption at 1070-1030 cm^{-1}, and glc analysis (column A) indicated the formation of several unidentified products.

Preparation of ketosulfoxide 39. A dry three-necked flask (300 ml) equipped with thermometer, addition funnel and a magnetic stirring bar, was charged with 50 ml of ether (dried over sodium), and dithioketal 38 (3.222 g, 9 mmol). This solution was cooled to -30°C and a solution of m-chloroperbenzoic acid (1.8 g of 85% mixture, 9 mmol) in 36 ml of ether was added slowly over a period of 1 hr. The mixture was stirred for an additional hour at this temperature, then diluted with 100 ml of ether and washed with 5% sodium bicarbonate solution, brine, and dried over $MgSO_4$. Evaporation of the ether yielded 3.3 g of the colorless viscous oil, which was chromato-

graphed over alumina (activity III) to give in order of elution: starting material (0.212 g, 7%), and then sulfoxide 39 (3 g, 89%), which had the following spectral properties: ir (liquid film): 1705 cm^{-1} (C=O), 1035 cm^{-1} (S=O); nmr (90 MHz, $CDCl_3$): δ 3.2-2.45 (m, 5H) ($\underline{CH_2}$-S)$_2$, $HC(-)$-C=O, 2.1-1.2 (m, 21H) $(CH_2)_9$, $\underline{CH_3}$-$C(-)$-S, 1.15-0.85 (m, 12H) methyl protons; chemical ionization (NH_3) mass spectrum showed the M^+ + 18 (m/e 392 peak).

Pyrolysis of ketosulfoxide 39. A neat sample of sulfoxide 39 (1.122 g, 3 mmol) was heated in a dry flask equipped with condenser and magnetic stirring bar at 85°C (bath temperature). The ir spectrum showed complete disappearance of the starting sulfoxide (1035 cm^{-1}) after one hour. The product mixture was diluted wtih ether (100 ml), washed with brine, and dried (K_2CO_3). Ether was evaporated and the resultant colorless oil (1.015 g) was chromatographed over neutral alumina (activity III). Elution with hexane resulted in the isolation of 0.44 g of a mixture of terminal and internal vinyl sulfides 37 and 30 (55%, 64:36 ratio); ir (liquid film) 1705 cm^{-1} (C=O), 1630 cm^{-1} (as a shoulder -$C(SR)$=CH-), 1605 cm^{-1} (CH_2=C-SR); nmr (90 MHz, CCl_4): δ 5.7-5.1 (two overlaping triplets, E and Z isomer 3:1) CH_3-C=$\underline{CH}$, 4.96, 4.61 (two doublets) $\underline{CH_2}$=C-SR, 2.8-2.45 (m, 3H) $\underline{CH_2}$-S, -$\underline{CH}(-)$-C=O, 1.1-0.8 (m, 9H) methyl protons; mass spectrum m/e:

268.1860 (calcd. for $C_{16}H_{28}O^{32}S$: 268.1861), 268(9), 179(3), 144(10), 143(100), 125(4). Elution with hexane-acetone (95:5) gave 0.215 g of diketone 24 (37%) which had identical nmr and ir spectra as that of an authentic sample.

Reaction of vinyl sulfides 30 and 37 with titanium tetrachloride. Titanium tetrachloride (0.26 ml, 2.4 mmol) was dissolved in 8 ml of glacial acetic acid. After 6 min at room temperature 0.268 g (1 mmol) of the mixture of the two vinyl sulfides 30 and 37 (1:18) dissolved in 2 ml of acetic acid was added and the resulting brown solution was stirred for 20 min. Then water (0.072 ml, 4 mmol) was added, and the reaction mixture was kept at room temperature for 4 hr. After this period it was poured into a cold saturated solution of potassium carbonate (30 ml), extracted with ether, and dried ($MgSO_4$). Evaporation of the solvent gave 0.24 g of yellow oil. Column chromatography over silica gel (200 mesh, hexane-chloroform 1:1 as eluent) yielded 0.053 g of diene sulfide 31 (21%), and 0.104 g of enone 25 (58%).

Cyclization of 2,6-dimethyl-6-(γ-n-butylthiocrotyl)-cyclohexanone using hydrochloric acid. To a solution of hydrochloric acid generated from acetyl chloride (20 mmol, 1.4 ml) and water (0.36 ml, 20 mmol) in 8 ml of acetic

acid was added 0.268 g (1 mmol) of vinyl sulfide 30 in 2 ml of acetic acid. The reaction mixture turned orange and then dark red. After stirring for 3 hr at room temperature it was quenched with cold saturated solution of potassium carbonate (30 ml), extracted with ether, and dried ($MgSO_4$). Chromatography over silica gel afforded 0.03 g of vinyl sulfide 31 (12%) and 0.12 g of enone 25 (67%).

Pyrolysis of sulfoxide 39 in the presence of potassium carbonate. A suspension of sulfoxide 39 (1.122 g, 3 mmol), and potassium carbonate (0.207 g, 1.5 mmol) was heated at 88°C (bath temp.) for 7 hr. After this period it was diluted with ether, washed with water, and dried (K_2CO_3). Evaporation of solvent gave 1 g of a yellow oil. The nmr spectrum of this crude mixture indicated formation of vinyl sulfides 30 and 37 (1:12). Purification over neutral alumina (activity III, hexane as eluent) yielded 0.695 g (87%) of a mixture of 30 and 37 (1:9); ir (liquid film): 1705 cm^{-1} (C=O), 1605 cm^{-1} (CH_2=C-SR); nmr (90 MHz, CCl_4) terminal isomer: δ 4.96, 4.6 (two doublets, 2H) $\underline{CH_2}$=C-SR, 2.8-2.45 (m, 3H)-$\underline{CH_2}$-S, $\underline{CH}$-C=O, 2.4-1.15 (m, 14H) $(CH_2)_7$, 1.1-0.8 (m, 9H) methyl protons.

Preparation of di-n-butylthioketal 42. A mixture of 2-octanone (6.4 g, 50 mmol), 50 ml dioxane, n-butyl mercaptan

(18.8 ml, 150 mmol), 20 g of zinc chloride, and 20 g of anhydrous sodium sulfate were stirred at room temperature for 5 hr. Then 30 ml of water was added, the mixture was extracted with chloroform, washed with sodium hydroxide (4 N), brine and dried ($MgSO_4$). Purification from alumina (act. III, hexane) gave 11.3 g (80%) of thioketal 42 as a colorless liquid; ir (liquid film): 1470 cm^{-1}; nmr (90 MHz, $CDCl_3$): δ 2.58 (t, 4H) $(-\underline{CH_2}-S)_2$, 1.8-1.15 (m, 21H) $(CH_2)_9$, $\underline{CH_3}-C\overset{-S-}{\underset{-S-}{\diagdown}}$ (as a singlet at 1.47), 1.1-0.8 (m, 9H) methyl protons; mass spectrum m/e 290.2099 (calcd. for $C_{16}H_{34}{}^{32}S_2$: 290.2102), 290(7), 201(100), 143(20), 111(13), 90(6), 89(2), 69(34), 57(9).

Preparation of monosulfoxide 43. Oxidation of 4.94 g (17 mmol) of thioketal 42 in 100 ml of ether using 3.45 g (17 mmol) of m-chloroperbenzoic acid was achieved following the same procedure described for the preparation of sulfoxide 39. After chromatography from a short alumina column, 4.68 g (90%) of a colorless oil was obtained; ir (liquid film): 1470, 1035 cm^{-1} (S=O); nmr (100 MHz, $CDCl_3$): δ 3.2-2.3 (m, 4H) $\underline{CH_2}$-S, $\underline{CH_2}$-S→O, 2.1-1.15 (m, 21H) $(CH_2)_9$, $\underline{CH_3}$-C-S, 1.1-0.85 (m, 9H) methyl protons; chemical ionization (NH_3) mass spectrum: M + 18 (m/3 324 peak); mass spectrum M-C_4H_9OS: 201.1674 (calcd. for $C_{12}H_{25}{}^{32}S$: 201.1676), 201(100), 200(18), 143(58), 111(31), 106(18), 90(2), 89(12), 69(71), 57(37).

Pyrolysis of monosulfoxide 43. A neat sample 1.533 g (5 mmol) of sulfoxide 43 was heated at 85°C for 1 1/2 hr, then dissolved in ether and washed with sodium bicarbonate, brine, and dried over potassium carbonate. Evaporation of solvent gave 1.47 g of a yellow liquid. Chromatography on alumina (activity III, hexane as eluent) afforded 0.7 g (70%) of a mixture (1:1) of the corresponding terminal and internal (E:Z, 1:1) vinyl sulfides 44 and 45; ir (liquid film) 1605 cm^{-1} (C=C), 1470 cm^{-1}; nmr (90 MHz, CCl_4): δ 5.6-5.15 (m) $CH_3-\overset{S}{\overset{|}{C}}=\underline{CH}$ (Z and E isomers), 4.93 (sharp triplet) $\underline{\overset{H}{H}}>C=C<^{S}$, 4.58(s) $\underline{\overset{H}{H}}>C=C<^{S}$, 2.6 (t, 2H) $\underline{CH_2}$-S, 1.15-0.8 (m, 6H); mass spectrum 200.1599 (calcd. for $C_{12}H_{24}{}^{32}S$: 200.1598), 200(38), 143(100), 115(31), 111(44), 110(22), 87(30), 74(87), 57(15),

Pyrolysis of sulfoxide 43 in the presence of potassium carbonate. A sample of compound 43 (1.533 g, 5 mmol) and potassium carbonate (0.415 g, 2.5 mmol) was heated at 94°C (bath temp.) for 5.5 hr. After this period it was diluted with ether, washed with water, and dried (K_2CO_3). Evaporation of solvent, followed by purification over alumina afforded 0.9 g of mixtures of 44 and 45 (3:1 ratio).

Reaction of sulfoxide 43 with triethylamine. Compound 43 (0.307 g, 1 mmol) was dissolved in 10 ml of triethyl-

amine and the resulting solution was refluxed overnight. After this period the mixture was dissolved in ether, washed with water and dried over potassium carbonate; after evaporation of solvent the nmr spectrum of the residue indicated formation of compounds 44 and 45 in 1.2:1 ratio.

Reaction of compound 43 with diisopropylethylamine. Sulfoxide 43 (0.307 g, 1 mmol) was dissolved in benzene (5 ml), 0.522 ml (3 mmol) of diisopropylethylamine was added and the mixture was refluxed for 17 hr (min. time required for the disappearance of S→O). Usual work up followed by nmr analysis showed that compounds 44 and 45 were formed in a 0.8:1 ratio.

Preparation of n-butyl vinyl ketone 50. A dry 300 ml three-necked flask equipped with a reflux condenser, dropping funnel, magnetic stirring bar, and N_2 inlet, was charged with 0.37 g (046.4 mmol) of powdered lithium hydride dispersed in 20 ml of anhydrous 1,2-dimethoxyethane. While this suspension was stirred, a solution of 4.0852 g (40 mmol) of valeric acid dissolved in 20 ml of DME was added dropwise. The resulting mixture was heated to reflux for 2.5 hr. Then the resulting suspension was cooled to approximately 10°C and vinyllithium (21 ml, 2.23 M) in THF was slowly added over a period of 30 min. The resulting suspension was

stirred at room temperature for 17 hr, and then siphoned into a vigorously stirred mixture of 7 ml (80 mmol) of concentrated hydrochloric acid, and 300 ml of water. The reaction flask was rinsed with 50 ml of pentane which was also added to the aqueous solution. The organic phase was separated and the aqueous phase was extracted with pentane. The combined organic extracts were washed with brine, and dried ($MgSO_4$). Removal of solvent and distillation of the residue yielded 2.6 g (60%) of compound 50 as a colorless liquid: bp 60-65°C (20 mm Hg); ir (liquid film): 1708, 1690 cm^{-1} (C=O, S-cis and S-trans), 1624 (C=C); nmr (90 MHz, $CDCl_3$): δ 6.45-6.2 (m, 2H) $\underline{H}\!>\!C\!=\!\underline{CH}\text{-}C(=O)$, 5.9-5.7 (m, 1H) $\underline{H}\!>\!C\!=\!C$, 2.56 (t, J = 7, 2H) $\underline{CH_2}\text{-}C(=O)$-, 1.8-1.1 (m, 4H) $(CH_2)_2$, 0.89 (t, J = 7, 3H) CH_3-.

Preparation of ethyl methylsulfinylmethyl sulfide 49.

To a solution of 2.484 g (2.1 ml, 20 mmol) of methyl methylsulfinylmethyl sulfide and 20 ml of THF, maintained under a nitrogen atmosphere at 2°C, was added slowly a solution of n-butyllithium (24 ml, 0.85 M, 20 mmol) in hexane, over a period of 30 min. The solution turned yellow after stirring for 30 min at this temperature. The mixture was warmed to room temperature and 2 ml (40 mmol) of methyl iodide was added. This reaction mixture was stirred at room temperature for 3.5 hr. After this

period, water was added and the mixture was extracted with methylene chloride, dried ($MgSO_4$), and evaporated. Chromatography over activity III alumina (hexane-acetone 9:1) yielded 2 g (73%) of compound 49 as a yellow oil; ir (liquid film): 1050 cm^{-1} (S→O); nmr (90 MHz, $CDCl_3$): δ 3.9-3.3 (m, 1H) CH, 2.62-2.5 (m, 3H) CH_3-S, 2.4-2.27 (m, 3H) CH_3-S, 1.65-1.45 (d, 3H) CH_3-CH.

Synthesis of ketosulfoxide 51. To a well stirred solution of 1.106 g (8 mmol) of sulfoxide 49 in THF (8 ml) at 0°C, was added 9.4 ml (8 mmol, 0.85 M) of a solution of n-butyllithium in hexane. The resulting solution was stirred at this temperature for 30 min, then cooled to -20°, and a solution of n-butyl vinylketone (0.887 g, 8 mmol) dissolved in THF (7 ml) was added. The resulting mixture was stirred at this temperature for 2 hr, then treated with saturated NH_4Cl solution, extracted with pentane and dried over K_2CO_3. Evaporation of solvent gave 1.67 g (84%) of crude 51, which was used as such in the next experiment without further purification; ir (liquid film): 1720 (C=O), 1050 cm^{-1} (S→O).

Pyrolysis of ketosulfoxide 51. A solution of 51 (0.25 g, 1 mmol) and potassium carbonate (0.153 g, 0.5 mmol) in 10 ml of toluene was refluxed for 17 hr. After usual work up and chromatography over silica gel (200 mesh, C_6H_6 as eluent) 109 g (58%) of vinyl sulfide 46a was

obtained (terminal to internal 95:5); ir (liquid film): 1720 (C=O), 1610 cm^{-1} (C=C); nmr (90 MHz, C_6D_6) terminal isomer: δ 4.97, 4.5 (two s, each 1H) $\underline{CH_2}$=C(S)-, 2.7-2.2 (m, 4H) -$\underline{CH_2}$-$\underline{CH_2}$-C(=O)-, 2.05-1.7 (m, 5H) - $\underline{CH_2}$-C(=O), $\underline{CH_3}$-S (as singlet at 1.83), 1.6-1.1 (m, 4H) $(CH_2)_2$, 0.9 (t, 3H) CH_3-; mass spectrum m/e: 186.1071 (calcd. for $C_{10}H_{18}O^{32}S$: 186.1078).

Thioketalization of levulinic acid. A mixture of 5.8 g (50 mmol) of levulinic acid, 22 g (20.5 ml, 200 mmol) thiophenol, and 0.25 g of p-toluenesulfonic acid monohydrate in 20 ml of toluene was heated under reflux for 24 hr. The toluene was distilled and the residue was dissolved in 200 ml of 90% aqueous methanol containing 20 g of potassium hydroxide. The solution was heated under reflux for 2 hr, then poured into an excess of cold, dilute hydrochloric acid. The mixture was extracted with benzene, washed with brine, dried ($MgSO_4$), and evaporated. Chromatography over silica gel (200 mesh, chloroform as eluent) yielded 8.52 g (50%) of the acid thioketal 52 as a colorless oil; ir (liquid film): 1715 (C=O), 750, 700 cm^{-1} (C_6H_5); nmr (90 MHz, $CDCl_3$): δ 11.5 (s, 1H) C(=O)-O$\underline{H}$, 7.76-7.55 (m, 4H), 7.45-7.2 (m, 6H) $(C_6H_5)_2$, 2.92-2.65 (m, 2H) $\underline{CH_2}$-C(=O), 2.2-1.93 (m, 2H) $\underline{CH_2}$-$C(SPh)_2$, 1.33 (s, 3H) $\underline{CH_3}$-$C(SPh)_2$; mass spectrum m/e: 318.0756 (calcd. for $C_{17}H_{18}O_2{}^{32}S_2$: 318.0749), 318(1), 209(100), 208(18), 191(16), 163(45), 135(30), 110(80),

109(35), 99(99).

Synthesis of ketothioketal 53 . A dry three-necked flask equipped with thermometer, magnetic stirring bar, dropping funnel, and N_2 inlet was charged with 4.77 g (15 mmol) of acid 52, and 80 ml of anhydrous ether. To this solution at -5°C was added a solution of n-butyllithium (25 ml, 33 mmol) in hexane, slowly over a period of 1 hr. The resulting suspension was stirred at room temperature for 4 hr, and then siphoned into a vigorously stirred mixture of ice, water, and hydrochloric acid. Extraction with ether, followed by drying over $MgSO_4$, and evaporation yielded 4.5 g of a yellow liquid, which upon chromatography over silica gel (200 mesh, benzene as eluent) gave 3 g (40%) of compound 53; ir (liquid film): 1720 (C=O) 750, 700 cm^{-1} (C_6H_5); nmr (90 MHz, $CDCl_3$), 7.73-7.5 (m, 4H), 7.4-7.2 (m, 6H) $(C_6H_5)_2$, 2.9-2.65 (m, 2H) $\underline{CH_2}$-C(=O), 2.35 (t, 2H) $\underline{CH_2}$-C(=O), 2.16-1.9 (m, 2H) $\underline{CH_2}$-$C(SPh)_2$, 1.7-1.0 (m, 7H) $(CH_2)_2$, $\underline{CH_3}$-$C(SPh)_2$ (as a singlet at 1.3), 0.87 (t, 3H) $\underline{CH_3}$; mass spectrum M^+ - C_6H_5S: 249.1309 (calcd. for $C_{15}H_{21}O^{32}S$: 249.1313), 249(66), 248(5), 191(2), 139(100).

Oxidation of thioketal 53. A solution of 1.79 g (5 mmol) of compound 53 in 50 ml of anhydrous ether was cooled to -78°C. To this was added 1 g (85%, 5 mmol) of m-chloroperbenzoic acid in 30 ml of ether over a period

of one hour. The reaction mixture was stirred at this temperature for 90 min, then diluted with ether (100 ml) and washed with 5% sodium bicarbonate solution, brine, and dried ($MgSO_4$). Evaporation at reduced pressure gave 1.7 g (91%) of the crude sulfoxide 54 which was used as such in the next experiment without further purification; ir (liquid film): 1720 (C=O) 1590 (C=C), 1050 (S→O), 750 and 700 cm^{-1} (C_6H_5).

Pyrolysis of ketosulfoxide 54. Compound 54 (1.7 g, 4.9 mmol) was dissolved in 10 ml of carbon tetrachloride. To this solution, 0.628 g (4.9 mmol) of potassium carbonate was added, and the suspension was heated at 60°C for 7 hr. Following the same work up procedure described for compound 43, and chromatography (activity III alumina, hexane as eluent) yielded 0.75 g (60%) of compound 46b (consisting of both regioisomers, 1:1 ratio); ir (liquid film): 1720 (C=O), 1640 (w) (C=CH), 1620 (M) (CH_2=C), 750 and 700 cm^{-1} (C_6H_5); nmr (90 MHz, CCl_4) δ 7.7-7.1 (m, 5H) C_6H_5, 5.92 (m) -$\dot{C}$=CH-, 5.13, 4.87 (two singlets) CH_2=C-SR; mass spectrum m/e 248.1236 (calcd. for $C_{15}H_{20}O^{32}S$: 248.1235).

Reaction of compound 46a with titanium tetrachloride. Titanium tetrachloride (0.13 ml, 1.2 mmol) was dissolved in 4 ml of glacial acetic acid, and after 5 min at room temperature a solution of 0.09 g(0.5 mmol) of compound

46a in 1 ml of acetic acid was added. The resulting mixture was stirred at room temperature for 20 min. Water (0.036 ml, 2 mmol) was added and the solution was stirred for an additional 3 hr. Then it was quenched with a cold saturated solution of potassium carbonate, extracted with ether, washed with water and dried. Evaporation of solvent followed by chromatography over silica gel (benzene as eluent) resulted in the isolation of 0.06 g (86%) of diketone 13.

Reaction of compound 46b with titanium tetrachloride. Using the same procedure as above, compound 46b (0.13 g, 0.5 mmol) was treated with titanium tetrachloride (0.13 ml, 1.2 mmol) in glacial acetic acid. After work up and purification over silica gel, 0.061 g (80%) of the diketone 13 was obtained.

Reaction of 2,5-nonanedione 13 with lithium diisopropylamide. Under an inert atmosphere (N_2), a solution of n-butyllithium (4.2 ml, 5.5 mmol) in hexane was added slowly to a stirred solution of diisopropylamine (0.6 g, 0.83 ml, 5.5 mmol) in 15 ml of anhydrous ether at -10°C. The temperature was held at -30° for 30 min, then cooled to -65°. A solution of 1,4-diketone 13 (0.78 g, 5 mmol) in ether (25 ml) was added very slowly over a period of 1 hr. After the addition was complete, the temperature was held at -40° for 1 hr. The resultant mixture was

hydrolyzed with acetic acid and extracted with ether. The organic layer was washed, dried ($MgSO_4$) and concentrated to give 0.71 g of yellow oil. Chromatography on silica gel (200 mesh, hexane-chloroform 1:1) yielded 0.395 g (50%) of starting diketone, and 0.27 g of an unidentified mixture of several products. Glc-mass spectral analysis (column B, 170°) of this portion indicated the presence of dimeric products.

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